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A STUDY OF THE RELATION OF THE ADRENAL GLANDS TO EXPERIMENTALLY PRODUCED HYPOTENSION (SHOCK); WITH A NOTE ON THE PROTECTIVE EFFECT OF PRELIMINARY ANESTHESIA

By Arnold Rice Rich

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In a study of the literature dealing with either surgical shock or the adrenal glands, one meets frequently the suggestion that shock may be the result of disordered function of the adrenals. This idea has been entertained especially as a corollary of the belief that, since epinephrin injected intravenously has such a remarkable effect upon the blood pressure, and removal of the glands brings about a condition of hypotension, the adrenals are therefore probably concerned in the maintenance of the blood pressure at the normal level. Since the condition of shock is characterized most strikingly by a marked fall in blood pressure, it has been suggested repeatedly that epinephrin exhaustion or adrenal fatigue may be causative factors.

Stewart and Rogoff [1] and others [2, 3] have shown that stimulation of the splanchnic nerves brings about an increased output of epinephrin from the adrenals. Hoskins and McClure [4] state that a similar effect can be produced by visceral exposure and operative trauma; Cannon and Hoskins [5] found that sensory stimulation increases the output of epinephrin, and Elliott [2] showed that the glands can in this way be quite depleted of their epinephrin content. Thus, it might be supposed that excessive intestinal or peritoneal manipulation or any severe prolonged sensory stimulation accompanying trauma may exhaust the epinephrin content of the adrenals and so bring about the condition of low blood pressure characteristic of shock. Indeed, the experiments of Corbett [3] and of Cannon and Hoskins [5] led them to make just this suggestion, although Cannon later [6] stated his belief that during shock "the adrenal glands are, if anything, over-active rather than exhausted." Quite a number of workers have reported that the epinephrin content of the adrenals is diminished by prolonged anesthesia, and it has been suggested that surgical shock may be dependent in part upon this epinephrin depletion.[7a]

Numerous attempts have been made to determine whether the supply of epinephrin is actually exhausted during shock, and whether abnormal variations in the epinephrin output

from the adrenals can be related to the development of shock. The results of these investigations are somewhat conflicting. Bainbridge and Parkinson[7] reported that they could find no epinephrin at all in the adrenals taken from fatal cases of post-operative shock, and this was confirmed by Elliott.[8] Short,[9] however, using a very delicate test, was unable to detect any reduction in the epinephrin content of adrenals taken from shock cases. Corbett[9] states that "the symptoms of shock fully develop only after the supply of epinephrin is greatly depleted," but he does not describe the experiments which led him to this conclusion. He does, however, report that animals which were subjected to prolonged sensory stimulation (sciatic) "very rapidly went into shock after a few minutes of peritoneal trauma" when the intestines were subsequently exposed, and he explains this by assuming that the preliminary sensory stimulation caused a reduction of the epinephrin supply. It is noteworthy in this connection that, in spite of numerous attempts, there is not a single convincing experiment on record in which true shock has been produced by the stimulation of sensory nerves. Sydenstricker, Delatour and Whipple[10] state that in animals which had been brought into the condition of shock by the injection of contents from a closed duodenal loop, determination of the epinephrin content of the adrenals disclosed only one-fourth of the normal amount, or even less. Bedford[11] reported that during shock produced by intestinal manipulation the epinephrin content of blood taken from the adrenal vein is much higher than before the onset of shock, and that the concentration increases with the prolongation of the low blood pressure. Stewart and Rogoff,[12] however, repeated Bedford's experiments with modifications in technique which they believe insure a greater accuracy in the estimation of the amount of epinephrin present in the blood, and they conclude that the output of epinephrin from the adrenals is the same during shock as it is under normal conditions.

Experiments such as these leave the question of the relation of the adrenals to shock in an unsatisfactory condition. In the first place, an altered epinephrin content of the adrenals or an abnormal output during shock might easily be a result rather than a cause of the condition. Thus Mann,[13] stating his belief that the adrenals enter as factors in the complex of shock, wrote that "it is quite difficult to determine to what degree they participate as primary agents in producing the state or how much they are affected by the low blood pressure and the changes incident to the condition itself." It might be thought that the removal of both adrenals would throw immediate light upon the theory of adrenal exhaustion; and indeed Crowe and Wislocki[13] have reported that following complete removal of both adrenals the animal gradually develops hypotension, rapid pulse, lowered body temperature, muscular weakness, apathy and dulled sensibility—all of which are characteristic of shock. On the other hand, it is claimed that adrenal extirpation does not really reproduce the condition of shock,[13] and Vincent[14] has even stated that experiments carried out in his laboratory demonstrate that a fall of blood pressure is not a characteristic effect of complete adrenalectomy. Furthermore, apart from the question of the effect of the mere removal o the adrenal glands, it is well known that there is a strong ten dency at the present time to believe that the adrenals normally play no direct part in regulating vascular tone,[14, 15, 16, 17, 18] or else that their activity is of value only in emergencies wher an unusual strain is thrown upon the circulation. If t latter supposition be true, it is clear that exhaustion of t adrenals during the strain of an operation or severe traum might deprive the animal of a protection of which the adrena ectomized animal, lying quietly in its corner, would have n need. Indeed, Abelous and Langlois[19] pointed out long a that muscular exertion following adrenalectomy hastens t development of the characteristic symptoms of adrenal defici ency. Thus it is evident that conclusions drawn from the effects of adrenalectomy alone cannot entirely satisfy the question of the relation of the adrenal glands to shock. The pres ent experiments were undertaken in the belief that if norma animals, subjected to a standardized trauma, fall into shock in a reasonably definite period of time, then worthwhile information might be obtained from a comparison of the protocols of these normal controls with the time required for the production of shock in adrenalectomized animals, subjected to the same trauma. For if shock results from epinephrin exhaustion or adrenal fatigue, the condition would presumably develop much more rapidly in the adrenalectomized animals than in the normal controls; if abnormal stimuli going to the glands cause an excessive output of some harmful material which produces shock, removal of the glands would remove the possibility of an outpouring of any noxious secretion and the adrenalectomized animals would be very resistant to the trauma; and finally, if the development of shock is independent of the activity of the glands, the adrenalectomized animals should react as normal animals to the same trauma. The fact tha bits of accessory adrenal and chromaffin tissue are present in animals has not been overlooked, but it was believed that the removal of both adrenal glands (the great bulk of such tissue) would produce a deficiency sufficient to be detected by this method of attack if adrenal function actually plays an important rôle in the production of shock.

Experiments

Certainly one of the most confusing things that one meets throughout the literature concerned with shock is the failure of many workers to standardize their experiments. Often, in a series of experiments where such precautions would be of value, no attempt is made to treat each animal in as nearly the same manner as possible either as regards the degree of trauma inflicted or (what is exceedingly important) the amount of anesthetic administered during the experiments. But especially is there a lack of a criterion as to what shall be regarded as shock. Thus, while most clinical and experimental observers incorporate a marked fall of blood pressure into their definition of shock, there are some whose experiments indicate that they do not regard such a fall of blood pressure as a necessary part of the picture. Wiggers[20] considers a fall of blood pressur a characteristic of "shock" produced by intestinal exposur

but he does not consider it an essential part of the "central nervous system shock" which he produced by sensory stimulation." This "central nervous system shock" is merely a condition of apathy and dulled sensibility and can occur with no important blood pressure fall. Doubtless some of the confusing experiments in the literature have arisen from a failure to recognize that this condition of apathy is not true shock. Mann [11] some years ago called attention to the need of a criterion for the condition of an experimental animal which should be regarded as shock, and his requirements followed admirably the signs which make up the clinical condition designated as shock.

In the present experiments, an animal was considered to be in shock when the blood pressure, having fallen to 60 mm. of mercury or below, showed no tendency to recovery and was accompanied by a permanent dulling of the sensibility, so that the ether could be discontinued without discomfort to the animal during operative procedures performed after a lapse of time (half an hour) sufficient to allow the anesthetic effect of the ether to wear off. Strong sensory stimulation applied to such an animal might cause struggling, but the animal would at once sink back into its quiet, apathetic state as soon as the stimulation was discontinued, although the abdominal contents were exposed and the neck opened for tracheotomy and cannulation of the carotid artery. A low blood pressure was required in these experiments because clinical shock without hypotension, although spoken of by a few writers,[12] is certainly an anomalous condition except in cases following head-wounds, and it is questionable whether such conditions are fundamentally the same as ordinary shock with hypotension. The level of 60 millimeters of mercury was arbitrarily chosen as a standard after a study of the average unrecoverable fall of blood pressure usually accompanied by a permanent dulling of the sensibility. The pulse of the animal in shock was usually rapid and feeble after the condition had persisted for some time, but frequently a marked slowing of the pulse was a prominent feature of the early stages, and periods of bradycardia have been observed during deep shock. The character of the respirations was very variable in the different experiments. The superficial reflexes remained active throughout, and the body temperature always fell several degrees centigrade more than did that of normal animals merely kept under ether anesthesia for the same period of time.

In all of the experiments described below apparently healthy, full grown cats were used and a careful attempt was made to subject each animal to conditions as nearly identical as possible as regards the trauma inflicted to produce shock and the amount of anesthetic used in each experiment. It must be stated here that during the progress of this work a number of animals were encountered which exhibited a peculiar sensitiveness to ether, so that the most careful administration of the anesthetic did not prevent them from behaving in a most anomalous way. The respirations would cease, and the blood pressure would fall abruptly shortly after anesthetization, and although artificial respiration would soon restore them, such lapses would occur repeatedly, and shock would appear much sooner than in normal animals. At autopsy no reason for the peculiar reaction was ever discovered. The number of such animals was relatively small, and it is felt justifiable to exclude them entirely from consideration, since they were clearly hypersensitive to the effect of ether alone.

Reaction of Normal Animals to Intestinal Manipulation.—The first series of experiments was carried out to determine whether normal animals would exhibit any constancy in the time required for the development of shock if they were subjected to a uniform trauma. Each animal was anesthetized with ether and tracheotomized. The tracheal cannula was connected through a reservoir with a tube through which ether vapor could be blown from an ether bottle by means of a foot bellows. As soon as the carotid artery could be cannulated and connected with a mercury manometer, a blood pressure tracing was made and the rectal temperature was recorded. Then the abdomen was opened at once along the midline, and the small intestines were lifted out of the abdominal cavity and spread upon gauze pads, care being taken to prevent torsion of the mesentery from interfering with the circulation. Every five minutes a blood pressure tracing was made, the temperature was recorded, the intestines were pinched firmly between the thumb and forefinger all the way from the duodenum to the cæcum once, and the animal received the amount of ether vapor which was forced into the reservoir by a single pump of the bellows. In the intervals between these procedures the animal was left to lie quietly. Usually a single pump of ether vapor sufficed to keep the animals anesthetized, and a second dose between the five-minute periods was administered only when necessary. The anesthesia was never deepened enough to abolish the corneal reflex. A careful control of the anesthetic is of great importance in such experiments, as may be seen from a consideration of Fig. 1. In this experiment a relatively large amount of ether was administered, with the result that the blood pressure fell to the shock level within a short while, and would have remained there, simulating the condition of shock, had not the ether been discontinued. Fifteen minutes after stopping the anesthetic the blood pressure began to rise and 10 minutes later had risen 40 millimeters more and the animal had regained full consciousness and sensibility. This effect of ether was repeated several times in the same animal, and demonstrated the necessity, in every experiment, of observing the animal for at least half an hour following the discontinuance of the anesthetic when shock is believed to have developed, in order to be certain that the low blood pressure and dulled sensibility are not ether-effects.

By following carefully the method outlined above, each animal received as nearly as possible the same degree of trauma and the same amount of anesthetic.

Inspection of the protocols and blood pressure tracings of this series of experiments shows that normal animals react to these conditions in a strikingly constant way. The blood pressure falls abruptly during the first five minutes after exposing the intestines and then, either continuously or after a temporary rise, it sinks gradually, with some irregularity, to the shock level, and the characteristic signs of shock make

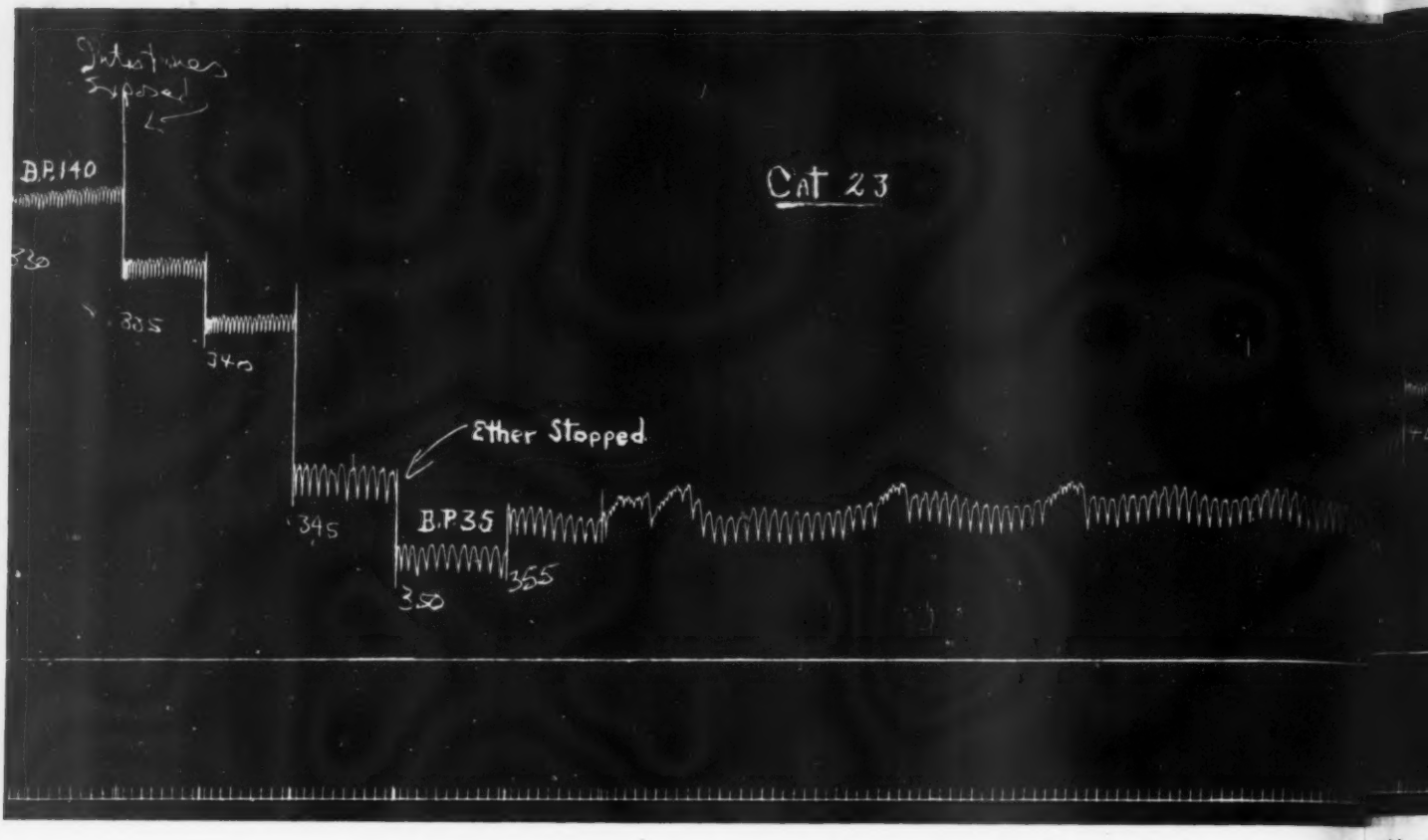


FIG. 1.—Careless anesthesia resulting in condition resembling with re

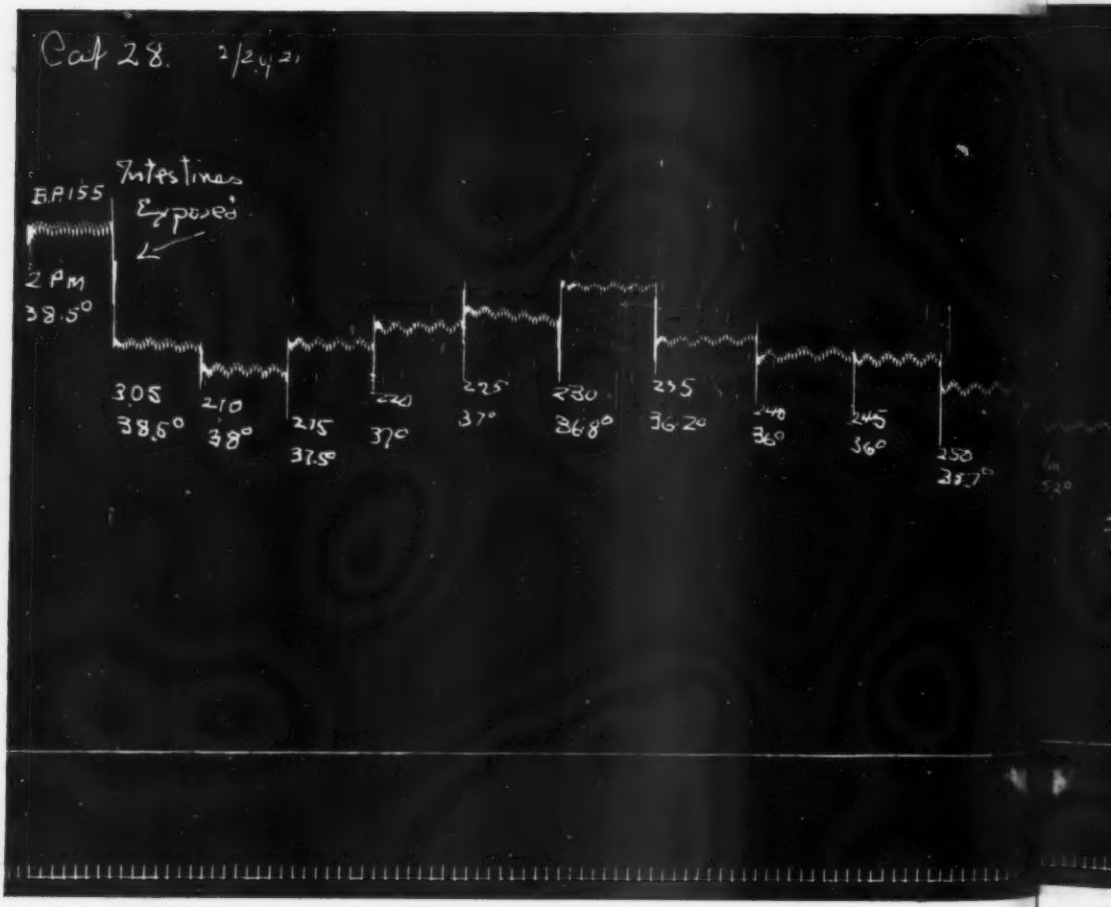
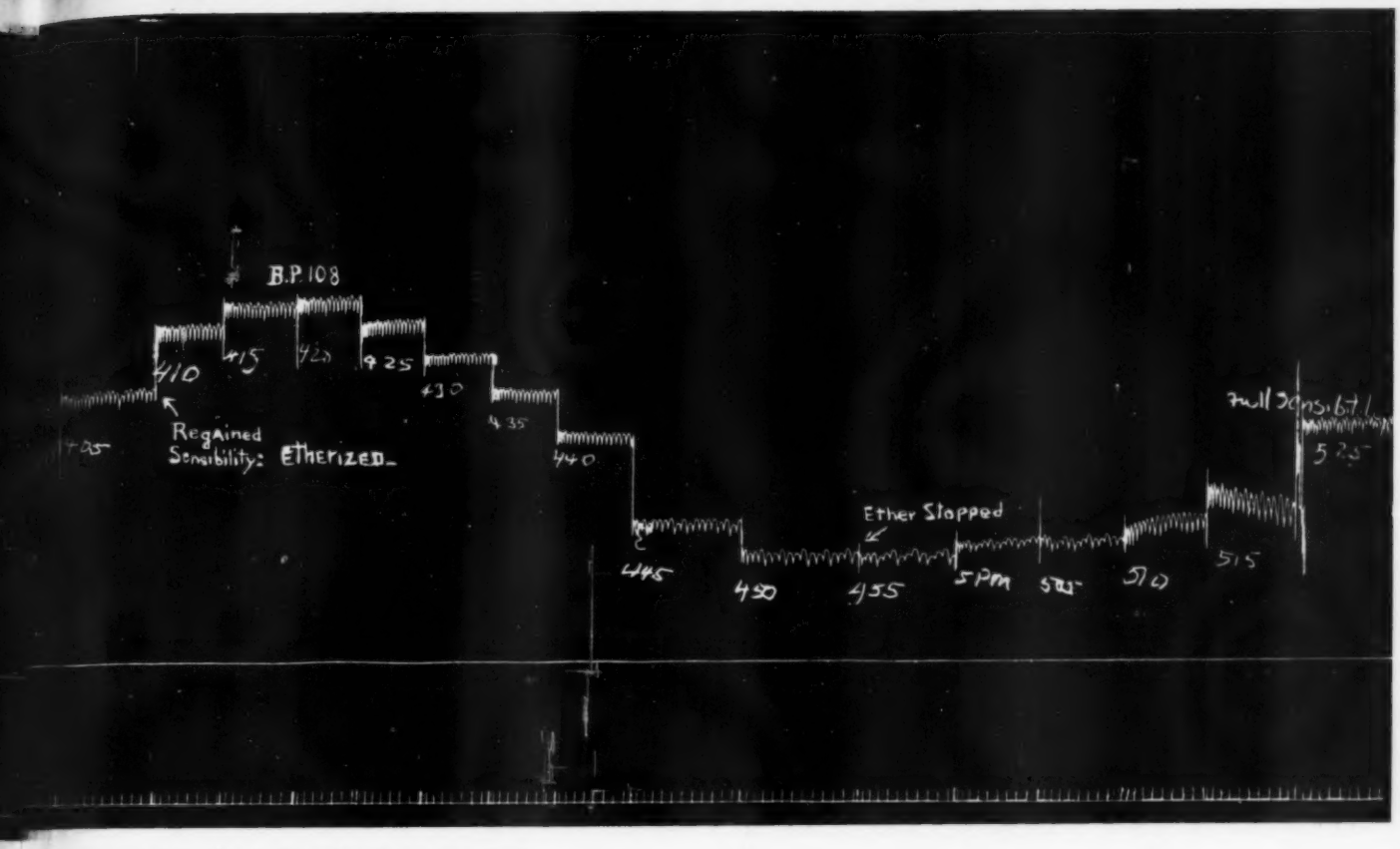
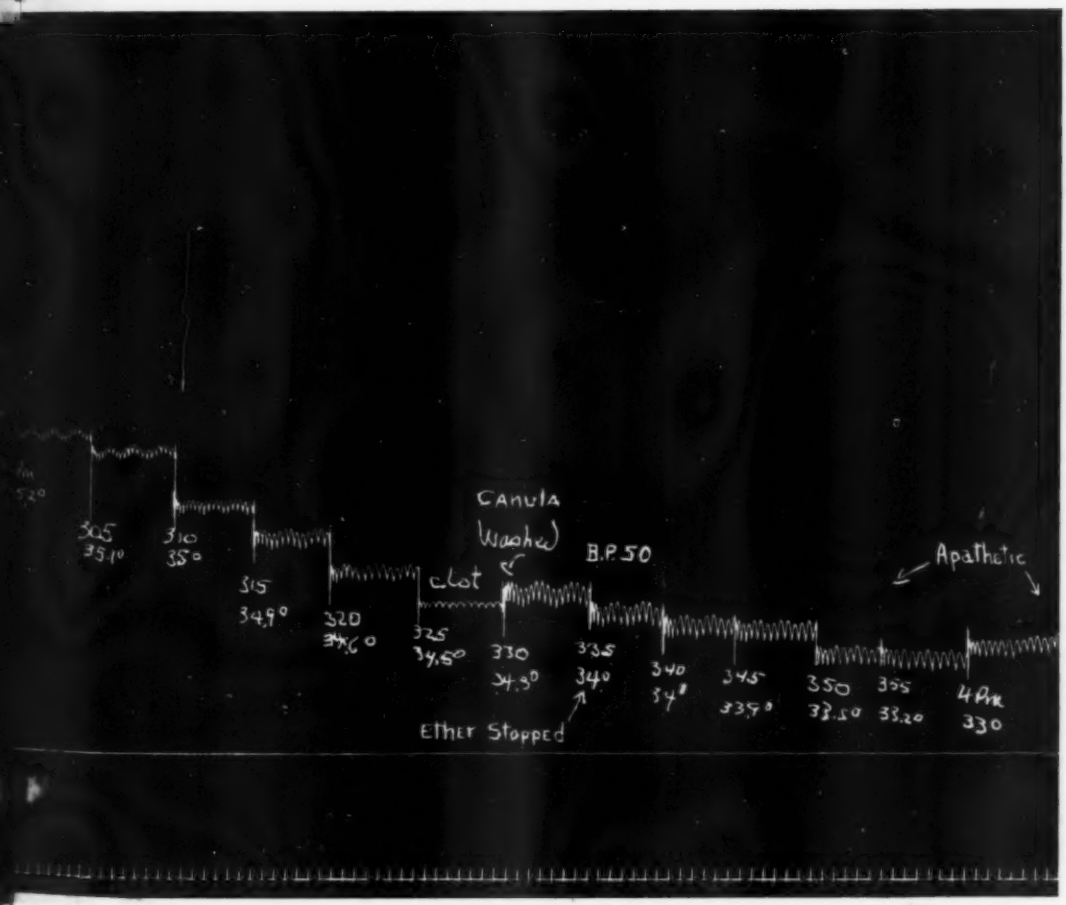


FIG. 2.—Blood pressure tracing of normal animal during production of shock by intestinal ation. S
pressure falls, a not infrequ ace in the



with recovery when ether is discontinued; not true shock.



ation. Shock present 1½ hours after exposing intestines. Note slowing of pulse as blood ace in the early stages of shock.

their appearance. The time required for the development of complete shock in these 10 animals was remarkably constant, varying between the extremes of an hour and a half and two hours, the average time being an hour and 50 minutes. Fig. 2 represents a typical experiment from this group.

Reaction of Animals Immediately Following Adrenalectomy.—Having determined the time required to bring normal animals into shock, we next carried out a series of experiments to study the reaction of adrenalectomized animals subjected to the same conditions. Each animal was anesthetized, tracheotomized and a blood pressure tracing taken just as in the first series. Then both adrenals were carefully removed extraperitoneally, and the lumbar incisions were closed with sutures. This procedure required 30 or 40 minutes and was performed with no more hæmorrhage than would stain part of a small piece of gauze. Kymographic tracings were taken every five minutes for about 20 minutes following removal of the glands in order to observe the immediate effect of the operation. During this time the blood pressure invariably either remained at the original level or, if anything, occasionally rose a few millimeters above it. The intestines were then exposed and manipulated exactly as in the normal controls, the method of anesthesia being the same throughout.

The reaction of these animals was most interesting. Kymographic tracings taken every five minutes, as before, showed that there occurred the usual slight fall of blood pressure immediately following the opening of the abdomen. This fall was promptly recovered from in several experiments; but in every experiment, during observations continued as long as two and a half and three hours following the exposure of the intestines, the blood pressure exhibited no further fall than the negligible depression which prolonged light anesthesia alone produces; and cessation of the anesthetic at the end of this time was invariably followed by prompt and complete recovery, although these animals were subjected to exactly the same conditions as the normal controls which were in deep shock, with the blood pressure at 60 millimeters or below, after only an hour and 50 minutes of intestinal manipulation. Fig. 3 is typical of this series. It will be seen that the blood pressure at the end of two hours and a half of intestinal manipulation stands at 110 millimeters, and has fallen from the original level no more than the blood pressure of normal animals kept quietly under ether anesthesia for the same length of time. The pulse is of splendid quality; and when the anesthetic was discontinued the animal promptly recovered full consciousness and sensibility. Not one of these 10 animals went into shock. Autopsy showed in every case complete removal of both adrenals.

This series of experiments seemed to favor strongly the idea that shock might be the result of some abnormal secretion of the adrenals, since there appeared no tendency for the condition to develop in adrenalectomized animals subjected to the same conditions which regularly produced it in the normal animal. There were, however, aside from the lack of adrenals, two points in which the adrenalectomized animals differed from the control animals at the beginning of the intestinal exposure—they had undergone an operation, and they had been kept under anesthesia for about an hour during the operation and the subsequent blood pressure observations made before the abdomen was opened. The fact that they had been subjected to an operation before beginning the shock trauma would be expected to increase their tendency to shock, if anything, and so too would a preliminary hour's anesthesia. A third series of experiments was carried out, however, to study the reaction of animals to intestinal manipulation following a preliminary hour's anesthesia alone.

Reaction After a Preliminary Hour's Anesthesia.—After tracheotomy and measurement of the blood pressure, the animals of this series were kept quietly under light anesthesia for an hour, kymographic tracings being taken every five minutes. Then the intestines were exposed and handled just as before. These animals reacted precisely as those of the adrenalectomized series; they showed no tendency to fall into shock during three hours of intestinal manipulation. Fig. 4 is a tracing from a typical experiment. The blood pressure shows no more tendency to fall after intestinal exposure than if the animal were merely kept anesthetized for the same length of time. Two hours and a half after the abdomen was opened the systolic pressure was 120 millimeters, the pulse was good, and when the anesthetic was discontinued, the animal regained full consciousness and sensibility and had to be killed. It will be noted that, in this particular experiment, besides the usual manipulation of the intestines every five minutes, considerable further trauma was inflicted without effect. The kidneys were roughly handled, several inches of intestine were resected at intervals, and the parietal and visceral peritoneum was stretched severely, with only a slight temporary effect upon the blood pressure.

In order to be certain that the resistance of these animals to shock was brought about by the preliminary hour's anesthesia rather than by some unrecognized technical divergence from the method used in the normal controls, two control experiments were now repeated, the intestines being exposed and handled immediately following the first blood pressure reading, instead of after an hour's anesthesia. These animals behaved exactly as the original normal controls. They were in deep shock in an hour and 55 minutes and two hours, respectively.

The 12 experiments with preliminary anesthesia were clear-cut, and demonstrated that an animal which has been kept anesthetized with ether for an hour immediately before opening the abdomen becomes, in some way, much more resistant to the shock-producing effects of intestinal manipulation than are animals in which the intestines are exposed more promptly after anesthetization. No explanation of the mechanism of this protective ether-effect can be offered here other than the suggestion that during the early stages of anesthesia the circulation appears to be in a rather unstable condition, and the added strain of visceral trauma at this period can, perhaps, bring about circulatory failure more easily than in an animal which has had time for its circulation to become accommodated to the state of anesthesia, and more stabilized. It is note-

worthy, however, that although an hour's light anesthesia *before* opening the abdomen had this protective effect upon the circulation, in other experiments it was clear that, once the blood pressure had begun to fall toward the shock level after intestinal manipulation had been begun, ether exerted a marked depressant action upon the circulation and distinctly favored the development of shock.

It is evident that no conclusions regarding the relation of the adrenals to shock could be drawn from the experiments in which the glands were removed immediately before exposing the intestines. The complicating factor of the protective ether-effect precluded that. It was, therefore, decided to remove the adrenals, to allow the animal to recover completely from the anesthetic, then to reanesthetize it afresh and proceed at once with the intestinal trauma.

Reaction Seven to Seventeen Hours after Adrenalectomy.—In this series of experiments both adrenals were removed extraperitoneally through lumbar incisions under strict aseptic precautions. The animals were then allowed to recover from the anesthetic and were left in their cages for periods ranging between 7 and 17 hours. None of the animals displayed any sign of adrenal insufficiency on inspection. They appeared active and not asthenic. Each animal was then anesthetized, tracheotomized, a blood pressure tracing taken and the intestines at once exposed and handled as usual. It was found at the outset that these adrenalectomized animals had a very low blood pressure, the first readings averaging 82 millimeters. The pulse was more rapid than normal. All of the animals of this series fell into deep shock within 30 or 35 minutes after exposure of the intestines, the blood pressure falling rapidly to 20 millimeters in most cases. At autopsy the operative sites were found in splendid condition, and dissection of the splanchnic nerves showed injury only to the small branches which necessarily must be severed in removing the adrenals.

Fig. 5 is a tracing from a typical experiment in this series.

Although these adrenalectomized animals went into shock in one-third the time required to bring a normal animal into shock, it was evident from the low blood pressure and rapid pulse that the circulation was already affected by the removal of the adrenals before intestinal manipulation was begun. It was not possible, therefore, to draw conclusions from this series concerning the relation of the adrenals to shock, and it was realized that experiments would have to be carried out upon adrenalectomized animals which had been allowed to recover from the anesthetic after adrenalectomy, in order to eliminate the protective ether-effect, but which had not been left long enough for circulatory signs of adrenal deficiency to appear before the animals were exposed to the shock-trauma.

Reaction One Hour After Adrenalectomy.—Since the blood pressure does not begin to decline until several hours after adrenalectomy, a series of experiments was carried out in which, following removal of both adrenals under aseptic precautions, each animal was allowed to recover fully from the anesthetic until it was able to walk about and to react normally to stimuli. In this way the protective effect of the anesthesia administered during the operation was avoided, since it had been determined in two experiments that if an animal were reanesthetized immediately after recovery from an hour's anesthesia, it retained none of the protective effect of the ether, but reacted to intestinal manipulation exactly as a normal animal. Complete recovery from the anesthetic administered during adrenalectomy required usually about 30 minutes; then the animal was reanesthetized at once, tracheotomized, and a blood pressure tracing made. The blood pressure was normal in every case, averaging 145 millimeters. The intestines were then exposed at once and handled as usual. These adrenalectomized animals reacted exactly as normal animals, requiring an average of an hour and 45 minutes to fall into shock. Fig. 6 is a typical tracing from this group.

This series of experiments indicates clearly that shock develops in the absence of the adrenal glands precisely and characteristically as it does in normal animals. Disordered function of the adrenals cannot be invoked as the cause of shock produced by peritoneal trauma. If the adrenals were causative factors of any importance, there would have appeared some difference between the reaction of the adrenalectomized animals and that of the normal controls. It might be objected that perhaps some of the secretion of the adrenals remains active in the body for a while after the glands are removed, so that adrenalectomy does not create an immediate deficiency of the secretion. It must be clear, however, that the same objection would be more applicable to any theory postulating disordered adrenal function as a cause of shock. The importance of the accessory chromaffin tissue is recognized fully, but since the adrenalectomized animals enter the experiment with complete absence of the adrenal glands, surely if epinephrin exhaustion or adrenal fatigue were causative factors in shock, these animals should fall into shock distinctly quicker than normal animals in which a longer time would be necessary to exhaust the greater epinephrin supply or bring the adrenal glands as well as the accessory tissue into a condition of dysfunction.

Condition of the Heart and Medullary Centers in Shock.—During the progress of these experiments advantage was taken of the opportunities to study the condition of various body functions during shock. Most observers have found that the heart functions normally during shock. Erlanger and his coworkers [29] acquired the impression that the heart in shock has not the normal reserve power and this might be expected, since Markwald and Starling have shown that weakening of the cardiac contraction accompanies low blood pressure.[30] Boise [31] attributed the circulatory failure in shock to impairment of cardiac function. In the present experiments the heart during shock has invariably worked splendidly both under the strain of large doses of adrenalin, and when normal saline was run rapidly into the jugular vein. In every experiment in which an animal was allowed to die in shock, respiratory rather than cardiac failure was the immediate cause of death.

It is almost universally stated that the pulse is rapid during shock. Wiggers, however, mentions slowing of the heart during the late stages of the condition [32] and Dupuytren [33] wrote from clinical observations "Le pouls est d'une lenteur et d'une

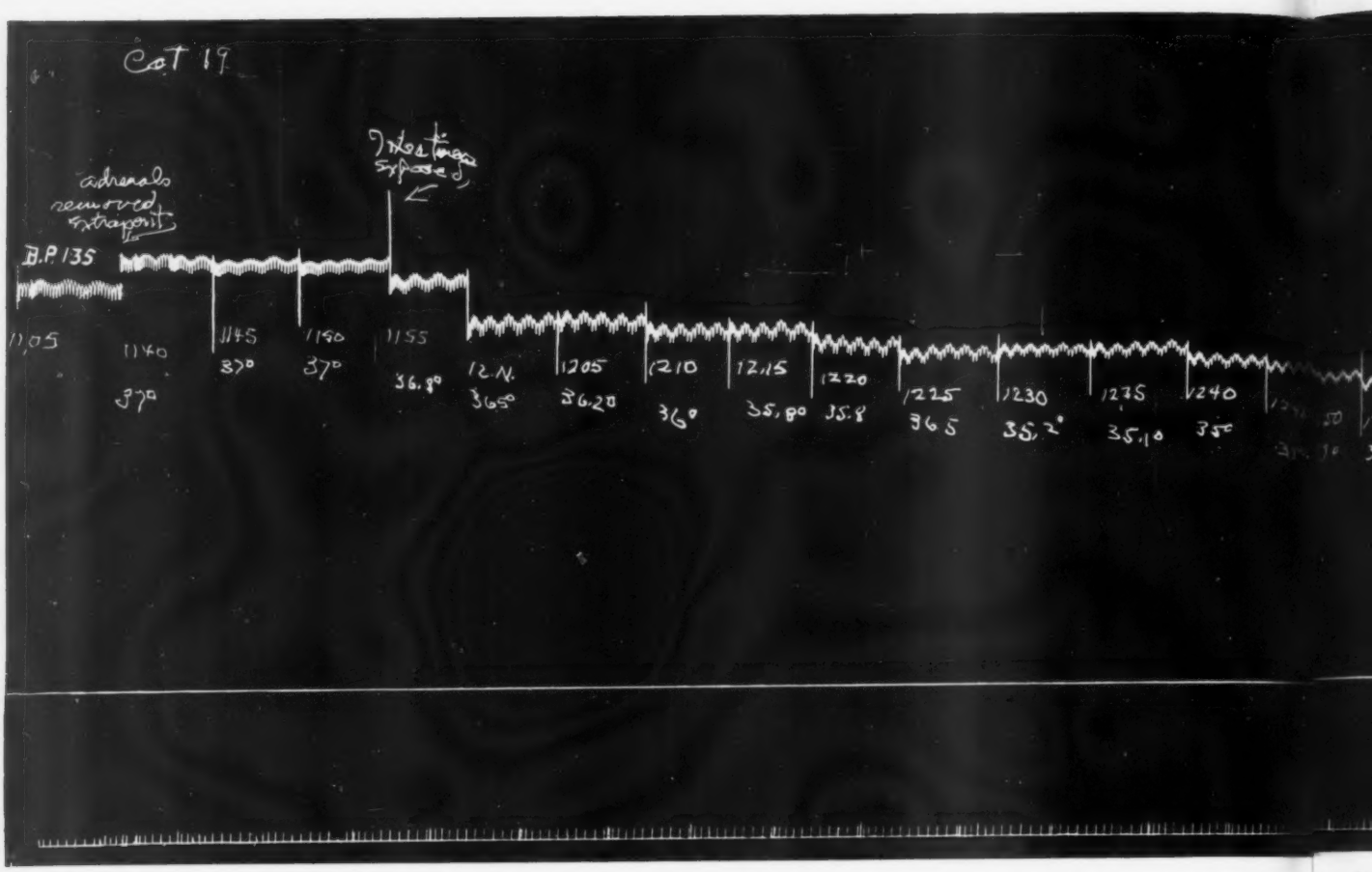


Fig. 3.—Adrenals removed at 11.40 a. m.; intestinal manipulation begun at [illegible] m. Co

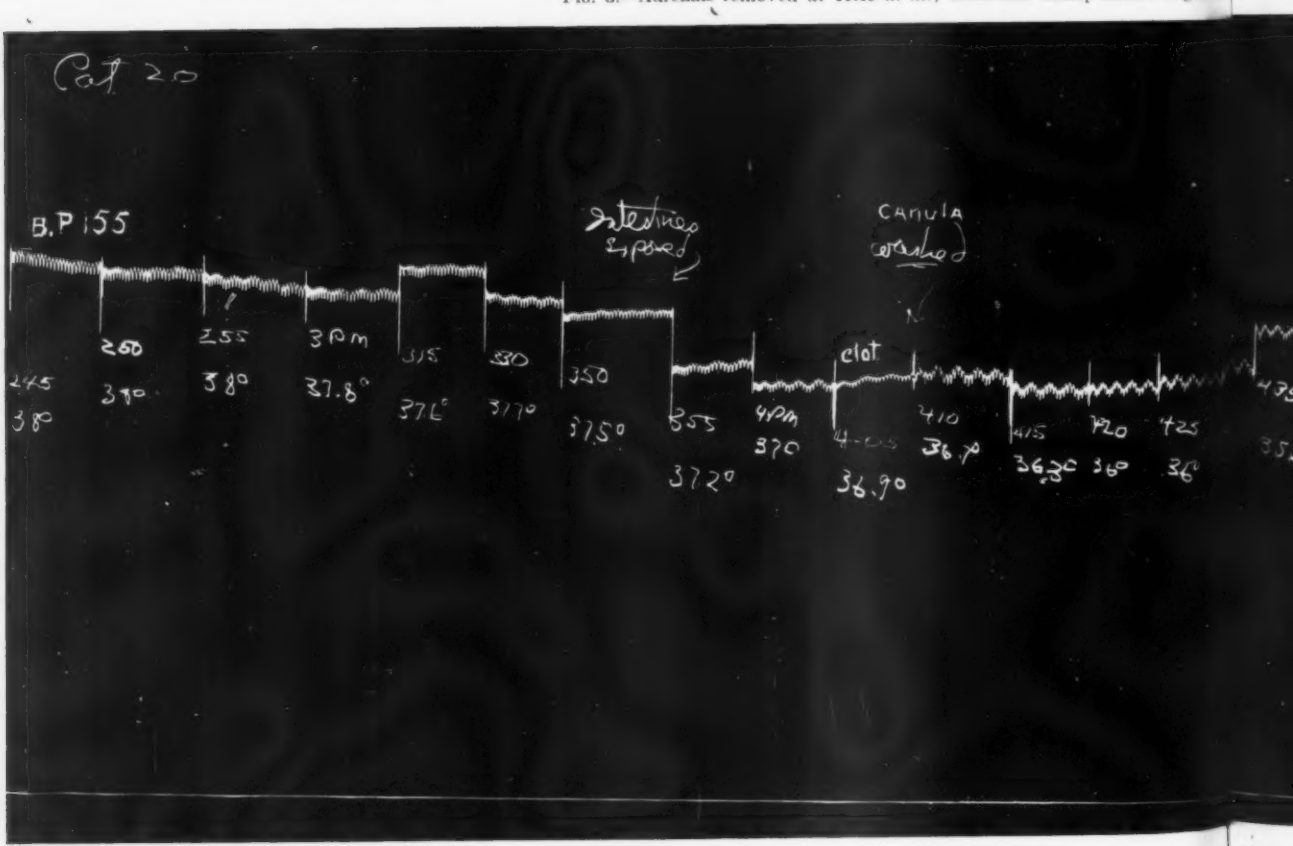
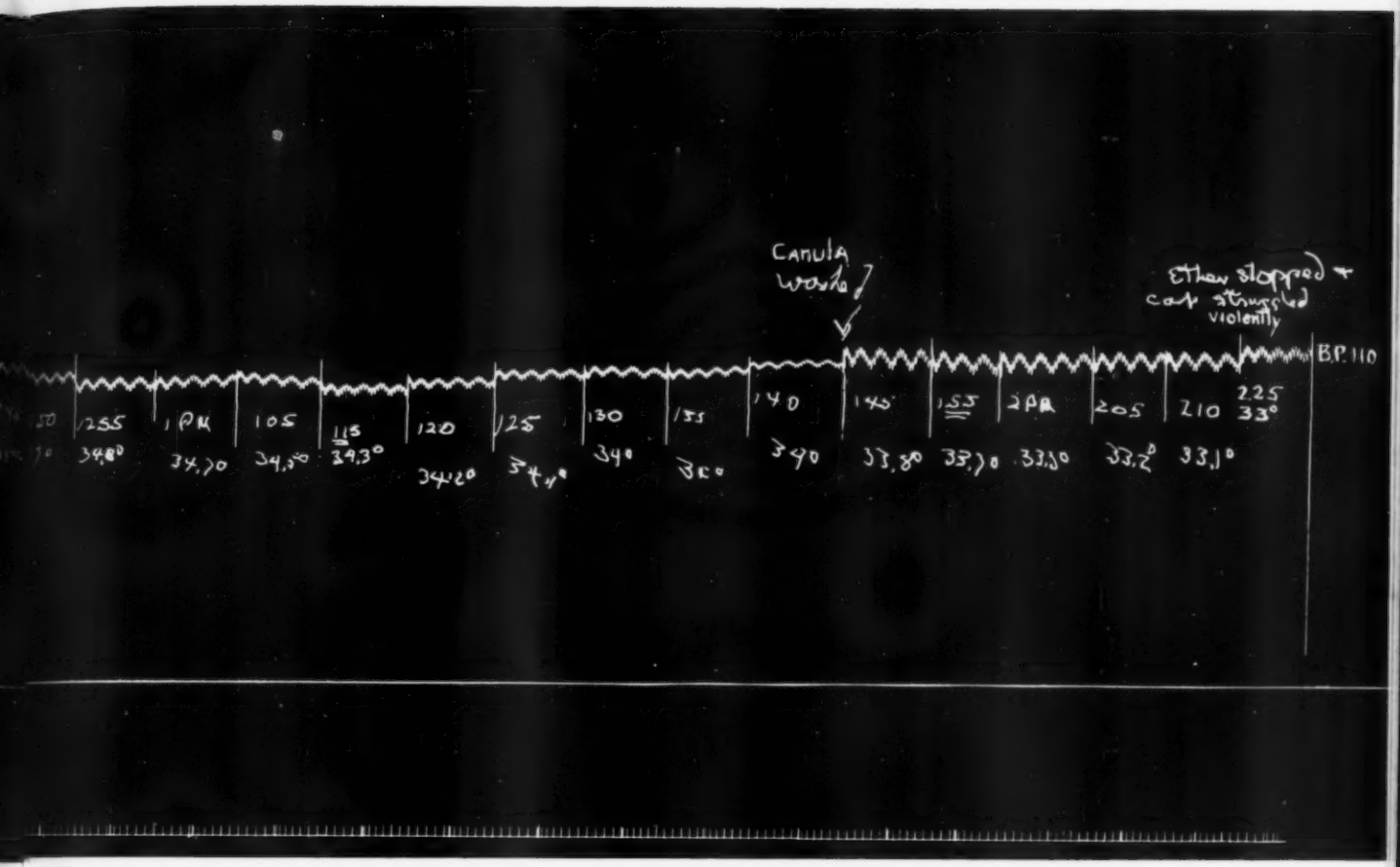
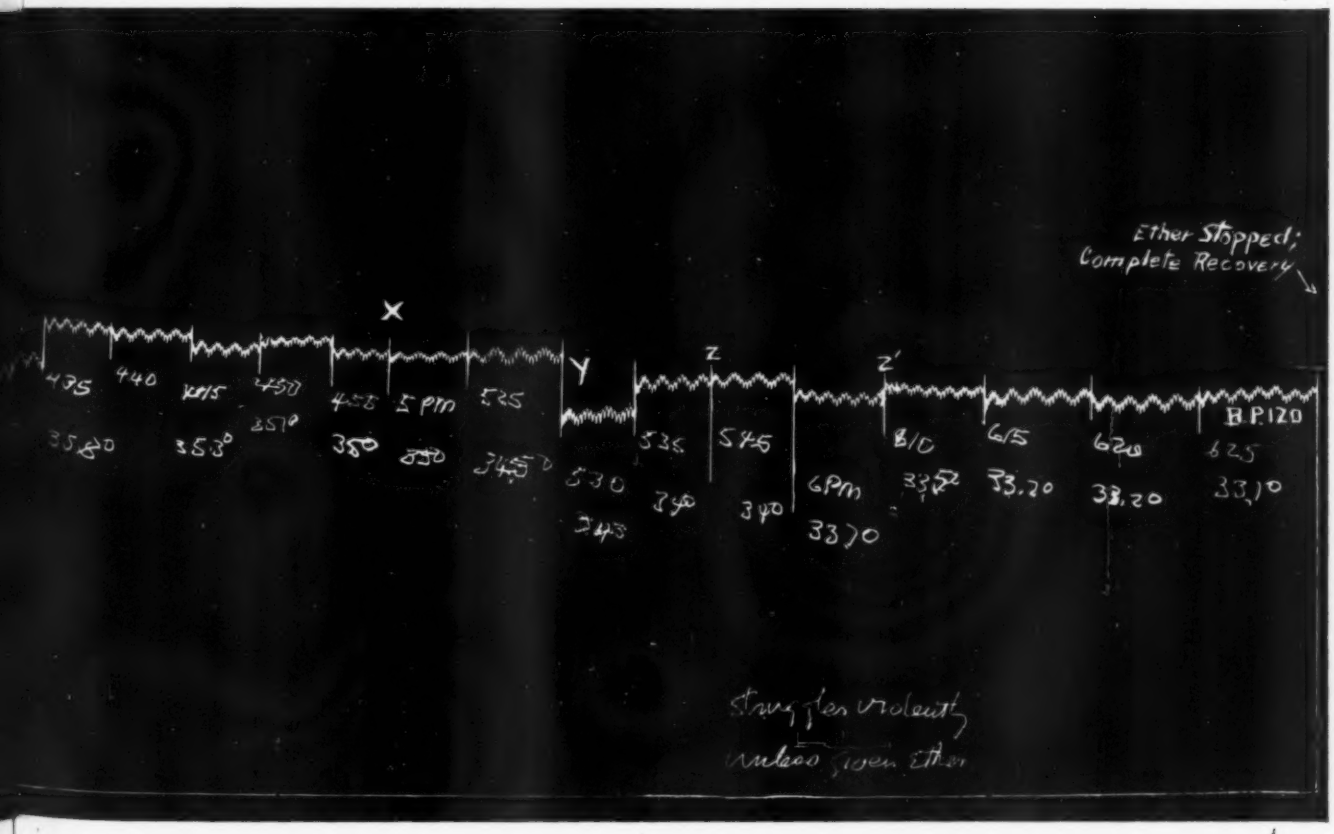


Fig. 4.—Intestinal manipulation after an hour's preliminary anesthesia. Besides the usual manipulation every 5 minutes, severe trac[illegible] the peri
Condition of animal [illegible] after 2½



at p. m. Condition of animal normal after 2½ hours of intestinal trauma. No shock.



the peritoneum and mesentery was made at *X*; kidneys roughly handled at *Y*; resection of several inches of intestine at *Z* and *Z'*. after 2½ hours. No shock.

mollesse telles que la plus légère pression le sufflamine," and that, if recovery takes place, "le pouls est plus fort et moins rare." In a number of the present experiments periods of pronounced slowing of the pulse were observed during deep shock. This slowing of the heart-beat is a result of the action of the cardio-inhibitory center. It has been held that inhibition or paralysis of this center is a characteristic and perhaps a cause of shock; on the other hand, the experiments of numerous workers indicate that the cardio-inhibitory center functions normally during shock. Mann reported that stimulation of the central end of one cut vagus caused reflex cardiac inhibition "even in the most extreme degrees of shock."[21] Jackson and Ewing wrote that they were able to obtain the reflex only while the blood pressure remained above 60 millimeters of mercury.[21] I have never failed to obtain slowing of the heart-beat during shock by this means, and the reflex has been elicited repeatedly when the blood pressure was as low as 20 millimeters (Fig. 7). In these experiments a further proof that the heart, in shock, is under control of the cardio-inhibitory center was obtained by observing the effect of cutting the vagi. If the vagi are sectioned during one of the periods of bradycardia which occur occasionally when an animal is in deep shock, a most striking acceleration of the pulse always results immediately, as can be seen in Fig. 8, where the heart-rate increased from 80 to 200 per minute. Section of the vagi when the pulse is rapid during shock will always increase the heart-rate unless it is already too rapid to be influenced by removal of vagus inhibition; and in the cases in which vagus section could not increase the rate, stimulation of the central end of one cut vagus has already produced slowing of the heart immediately before section of the remaining vagus, showing that the cardio-inhibitory center was capable of responding to stimuli during shock. In three experiments both vagi were sectioned before exposing the intestines; these animals went into shock no more rapidly than the normal controls, and their blood pressure curves were characteristic of the normal shock curves. It is clear that failure of the cardio-inhibitory center is not a causative factor in shock.

The question of the condition of the vasomotor center has been the subject of many investigations. On the basis of their well-known experiments, Crile,[24] Lockhart-Mummery[25] and others have maintained vigorously that surgical shock represents an exhaustion of the vasomotor center; others[20, 27, 29, 21] have produced splendid evidence that it is not exhausted. In the present experiment, a pressor response could always be elicited by stimulation of sensory nerves during shock. In most of the experiments the rise of blood pressure was less prompt and less marked than before the onset of shock, although in some cases the rise was quite as marked. Fig. 9 shows a definite pressor response obtained by sciatic stimulation during deep shock, when the blood pressure was only 22 millimeters. I can entirely agree with those who hold that exhaustion of the vasomotor center is not a primary factor in shock.

Janeway and Ewing[17] have stated that in shock produced by intestinal manipulation "there is absolute paralysis of every tissue of the intestines, of the muscles, of the intestinal walls and of the arterioles," and they stress the importance of a local peripheral paralysis of the splanchnics as a factor in shock. I have never observed such a complete paralysis of the intestines during shock. Abortive peristaltic movements occur throughout the duration of shock, and not infrequently persist for a short while after death. Janeway and Ewing wrote that in some of their experiments the intestinal manipulation was quite violent, causing rhexis of the peritoneum. It is possible that excessive trauma might produce such a paralysis, but surely it cannot be regarded as a characteristic part of shock.

The Hypotension Resulting from Adrenalectomy.—It may not be entirely out of place here to describe several observations upon the group of adrenalectomized animals which may have some bearing upon the function of the adrenal glands.

In the first place, although we have the clinical evidence of Addison's disease and certain experimental evidence besides, indicating some relation of the adrenal glands to the maintenance of normal blood pressure, Vincent[14] reports that continous blood pressure tracings, taken up to the moment of death, after complete removal of the adrenals from the circulation, show no greater fall in blood pressure than would have occurred in a normal animal subjected to ether anesthesia alone for the same period of time, and he concludes that "these experiments appear to show conclusively that the secretion of adrenalin into the circulation is not to be regarded as a factor in the maintenance of the normal blood pressure." The present experiments do not at all agree with such an observation. Howell[13] and others have pointed out that adrenalectomy has no effect upon the blood pressure for several hours, and I have observed this fact repeatedly. But the blood pressure of an adrenalectomized cat begins to fall gradually about four hours after the glands have been removed, and within the first 12 hours after adrenalectomy the blood pressure in the unanesthetized animal invariably falls to a very low level and continues to decline progressively until death. In these experiments it was demonstrated that the marked hypotension, observed in every case as early as seven hours after adrenalectomy, is a characteristic result of adrenal deficiency and not merely a condition of lowered tone in an animal several hours after an operation. For in a number of experiments both adrenals were exposed aseptically and handled even longer than would have been necessary to remove them. They were then left in their normal positions and the incisions closed. Seven to twelve hours later these animals were reanesthetized and the blood pressure in every case was normal and exposure of their intestines produced shock in the length of time characteristic of normal animals. In another series, under aseptic precautions, one adrenal was removed and the other exposed and handled, the operation taking as long as if both had been removed and the operative trauma being made purposely more severe. When these animals were reanesthetized after a lapse of from 7 to 15 hours, their blood pressure was found to be normal and they reacted to intestinal manipulation exactly as normal controls. Autopsy showed complete removal of one

adrenal in every case. Thus, the trauma of the operation alone is not responsible for the low blood pressure which developed in every completely adrenalectomized animal; nor has removal of one adrenal any effect upon the blood pressure during the period of these experiments; but when both glands are removed the blood pressure invariably falls strikingly. The splanchnic nerves were dissected at autopsy in every case in order to make certain that injury was confined only to the little branches which must be cut in order to remove the adrenals. I cannot agree with those who have claimed that the low blood pressure developing after adrenalectomy is merely the hypotension to be observed in any moribund animal, nor does the contention of Hoskins and McClure,[4, 11] that the hypotension is a result of asthenia, seem reasonable; for these adrenalectomized animals were by no means in a moribund condition, nor was there evident asthenia seven hours after removal of the glands. One of these adrenalectomized animals, a rather wild male, escaped from its cage just before it was anesthetized for the blood pressure reading and ran swiftly about the room, evading capture. It was caught, anesthetized, and the systolic pressure found to be 75. It seems more reasonable to believe that the hypotension leads finally to asthenia because of the impairment of the circulation.

The fact that hypotension is a characteristic effect of adrenalectomy and that it appears to be the result neither of the trauma of the operation nor of the asthenia, supports the belief that the adrenals are, after all, directly concerned in some way in the maintenance of normal blood pressure. This idea is strengthened by observations upon the powers of resistance of the circulation of adrenalectomized animals to strains (such as prolonged anesthesia and trauma) imposed upon it. These experiments are as yet incomplete, but they strongly suggest that the circulation of an adrenalectomized animal, after the development of hypotension but before the appearance of asthenia, is distinctly more unstable than that of a non-adrenalectomized animal with the same degree of hypotension.

DISCUSSION

It may possibly appear inconsistent that any observations supporting the belief of the activity of the adrenals in maintaining normal blood pressure are presented here together with evidence that these glands are not concerned in the circulatory failure characteristic of shock; but certainly, even though the adrenals be concerned with blood pressure regulation, they are not by any means the only factor involved. The demonstration of the lack of any causal relation between the adrenals and the acute hypotension of shock merely points more distinctly to a disturbance of some other part of the intricate circulatory mechanism.

At the present time, the idea that the adrenals may be concerned with the maintenance of normal blood pressure is widely repudiated, and the work of Cannon, Gley, Stewart and Rogoff, Hoskins and McClure, and Vincent, in this connection is familiar enough to everyone who has given any attention to the function of these glands. The objection has been repeatedly brought forth that if adrenalin were necessary for the maintenance of normal blood pressure, removal of the glands should result in an *immediate* fall of pressure; but no fall occurs during several hours after adrenalectomy.[14, 33, 36, 37] Much has been made, also, of the fact that adrenalin can be detected in normal blood in minute amounts only; so minute, indeed, that numerous writers do not hesitate to declare that it is physiologically useless in affecting vasomotor tone, especially since the intravenous injection of small amounts of adrenalin can produce a depressor instead of a pressor effect.[35, 35, 35, 35] Perhaps these, and certain other similar observations which cannot be discussed here, deserve more critical consideration and study before they can be accepted as reasons for believing that adrenalin plays no part in the maintenance of normal arterial pressure, or that "l'adrénaline ne doit plus être considérée comme un produit de secrétion vraie."[35]

In regard to the objection that the blood pressure does not fall *immediately* after adrenalectomy (and some have actually been content with blood pressure observations continued less than two minutes after compression of the adrenal veins)[37] it does not seem permissible to ignore completely the fact that there is a definite supply of physiologically active epinephrin left in the accessory chromaffin tissue after removal of the adrenal glands,[20, 38] and that this supply may be sufficient to sustain the blood pressure for several hours, but not indefinitely. It is true that Stewart and Rogoff have considered this point to the extent of writing: "No account is here taken of the possibility that the sporadic chromaffin tissue may discharge a certain amount of epinephrin, since, although it has been shown to contain that substance, nothing is known as to its liberation";[20] however, the fact of our ignorance as to the mode of liberation of epinephrin from this accessory chromaffin tissue is not a satisfactory reason for taking no account of it. The well known protective effect of minute residual fragments of parathyroid,[39] thyroid and adrenal[40] tissue left, either intentionally or by accident, in extirpation experiments demonstrates strikingly enough the rôle that a relatively insignificant amount of such tissue can play. It is curious, in any event, that those who feel that the adrenals have nothing directly to do with vascular tone, because hypotension does not occur the instant the adrenal veins are clamped, nevertheless appear to accept the belief that the glands are concerned in some way with the maintenance of muscular tone, although asthenia develops, after adrenalectomy, distinctly later than hypotension. It seems to the writer that the important fact may be, not that the blood pressure fails to fall immediately after removal of the glands, but rather that a primary effect of adrenalectomy is hypotension.

Concerning the minute amount of epinephrin that can be detected in the blood, it is difficult to be sure that it has no physiological significance in relation to normal blood pressure simply because the amount collected at any given moment is too small to affect the contractions of a strip of smooth muscle *in vitro*, or to exert a pressor effect upon the blood pressure when introduced into the circulation of an animal. Unquestionably, such procedures appear to be surprisingly delicate quantitative tests for the presence of epinephrin within wide

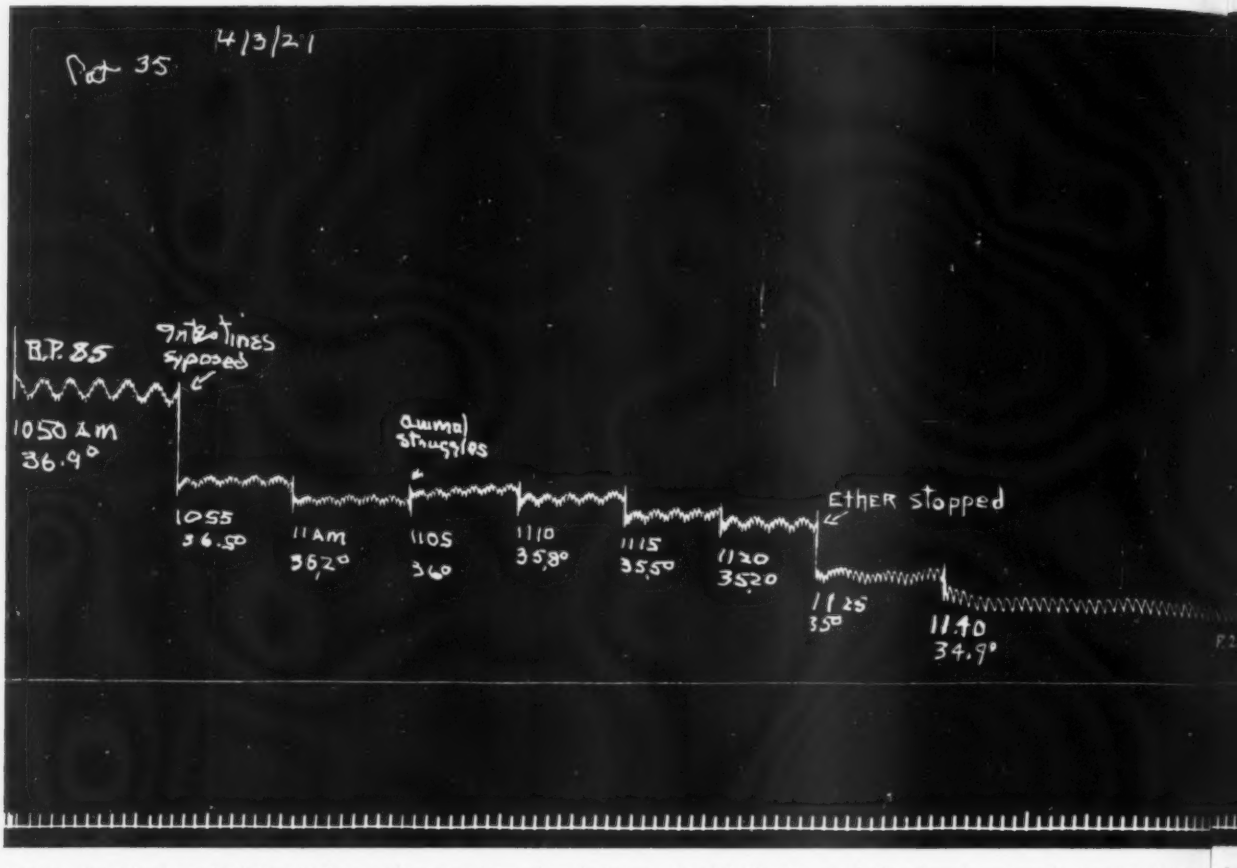


FIG. 5.—Intestinal manipulation 11 hours after complete adrenalectomy. April 2, 11.50 p. m., both adrenals removed; April 3, 10.40 a. m. animal about, apparently normal. Intestines exposed 10.55. Deep shock 30 minutes later.

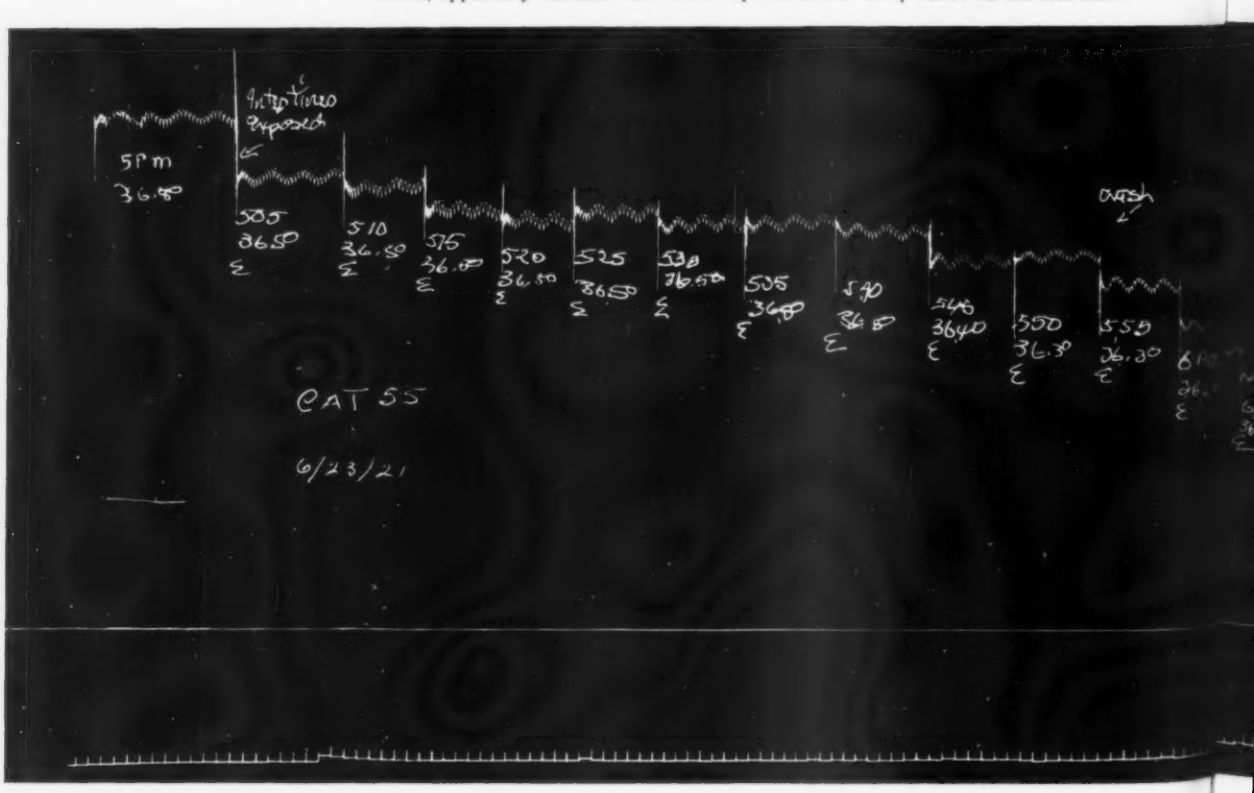


FIG. 6.—Intestinal manipulation 1 hour after adrenalectomy. June 23, 3.30 p. m., operation for removal of both adrenals begun; off table 4 m.

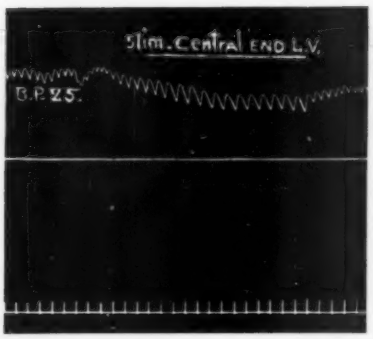


FIG. 7.—Slowing of the heart produced during deep shock by stimulating central end of cut left vagus (B. P. 25).

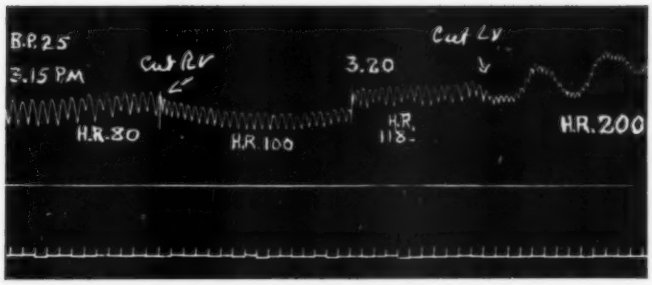
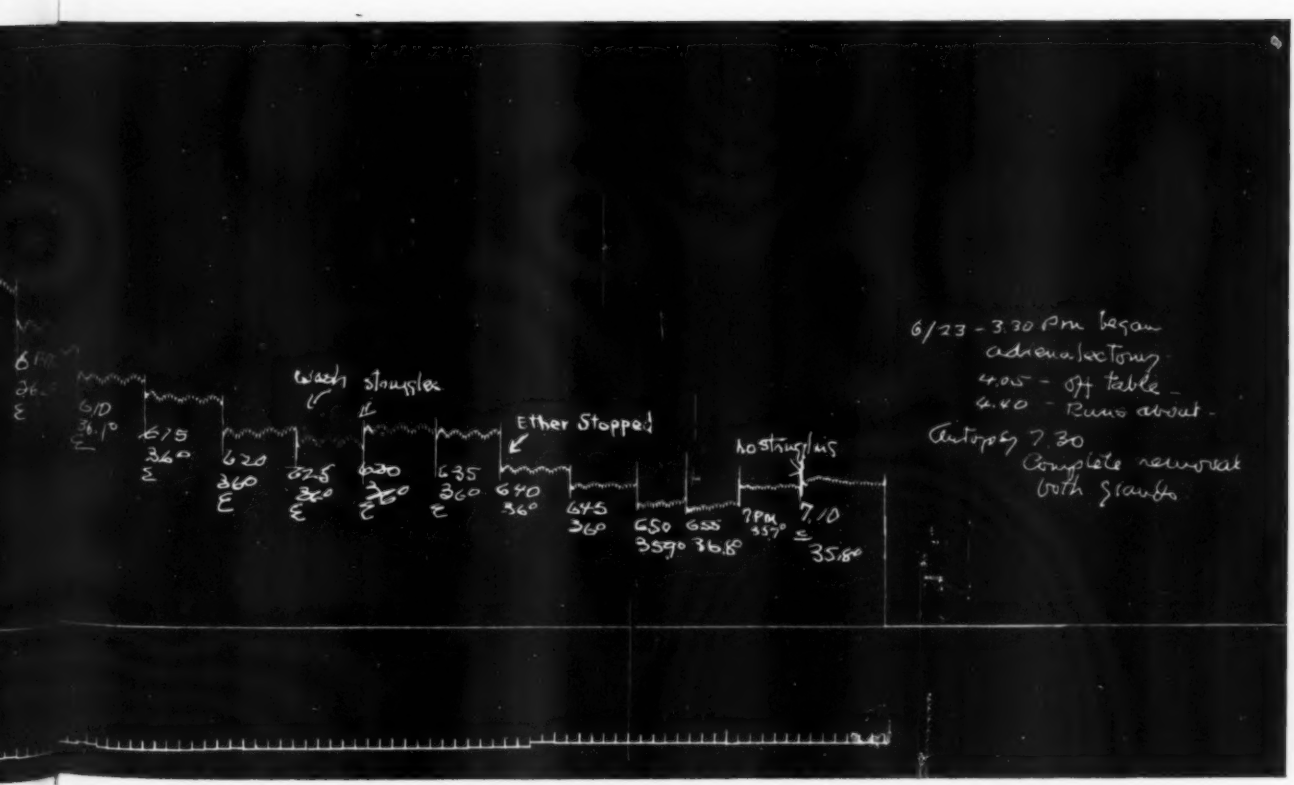


FIG. 8.—Shows activity of cardio-inhibitory center producing spontaneous bradycardia during deep shock. Heart rate increases from 80 to 200 per minute on section of vagi.

FIG. 9.—Pressor response elicited by stimulation of sciatic nerve during deep shock (B. P. 22).

10.40 a. m. final runs



off table 5.05 p. m. Complete recovery from anesthetic at 4.40 p. m. Intestines exposed at 5.05 p. m. Shock 1 hour 35 minutes later. Compare with Fig. 2.

limits; however, they have limitations, a point which Stewart and Rogoff did not ignore when they concluded from certain experiments that the "liberation of epinephrin from the adrenals is not indispensable for life or health, unless indeed the necessary quantity is, even in the adrenal vein blood, below the limits of detection by the methods used."[1] The fact that the quantity of epinephrin in the blood, at any given time, is minute or even indetectable by present methods (Stewart and Rogoff, however, do detect it unfailingly in normal adrenal vein blood) does not entirely satisfy the question of the relation of this substance to normal blood pressure. In the first place, the methods of collecting and assaying the blood samples and the conditions under which the blood is obtained are apparently so subject to error that almost each worker has devoted some space in the literature to a more or less caustic criticism of the other's technique: and in the second place, it is highly probable that there may be a difference between the physiological potentialities of minute amounts of a substance secreted continually, and the effects which can be demonstrated when the amount that is withdrawn from the circulation at any one cross-section of time is used in an acute experiment. Otherwise, we would have to conclude from a study of small samples of normal arterial blood that the secretion of the thyroid gland has no effect upon body oxidations, and that of the para-thyroids no relation to calcium metabolism.

The most elaborate and important recent work on the adrenals[1, 2, 3, 4] has been concentrated upon the question of the existence of a physiological adrenalinaemia, and has been concerned not at all with the fact that the most striking primary effect of the lack of the adrenal secretion is hypotension. Unquestionably, the painstaking and ingenious experiments of these workers hold a very great interest. Because of the ease with which epinephrin can be detected, the study of the epinephrin content of the blood promised much, and it was most important that it be carried out. However, it is perhaps permissible to feel that this study, even in the hands of such able investigators, has not led to conclusions as concordant or decisive as one might have hoped for. It must be remembered that there still exists an active controversy between these workers over the amount of epinephrin normally present in the blood, and also over the more important question of whether the epinephrin content of the blood is increased during the various reflex pressor reactions which have been assumed to be conditioned or influenced by an outpouring of this secretion. The only point of agreement, in fact, seems to be the opinion that the amount of epinephrin circulating normally is not great enough to exert an influence upon normal blood pressure. It is quite possible that epinephrin has nothing to do with the maintenance of normal pressure, as these observers insist; it may, indeed, be that the lack of the unknown cortical secretion is responsible in some way for the hypotension that follows adrenalectomy. Nevertheless, the observations leading to a denial of any relation of epinephrin to normal arterial pressure have certainly not yet settled this important question, which must remain incompletely answered until we are able to understand why the blood pressure falls so characteristically when the adrenal glands are removed from the body.

Summary

I. Adrenalectomized animals, subjected to uniform intestinal manipulation before the blood pressure has begun to decline as a result of adrenalectomy, fall into shock exactly as do normal controls—the time required for the production of shock and the character of the blood pressure curves being the same in both series. It is therefore concluded that disordered adrenal function is not a factor in the production of shock.

II. Hypotension invariably results from removal of the adrenal glands, and with the development of hypotension the circulation of adrenalectomized animals appears to become more unstable than that of normal animals even before the appearance of asthenia. The blood pressure begins to fall several hours after adrenalectomy and becomes progressively lower until death. The fall in blood pressure is shown to be independent of the operative trauma and begins before asthenia has appeared. This is offered in support of the idea that the adrenals are concerned in the maintenance of the blood pressure at the normal level, and certain objections to this belief are briefly discussed.

III. Animals that are kept lightly anesthetized with ether, for an hour immediately before the abdomen is opened, become very resistant to the shock-producing effect of intestinal manipulation. Even when subjected to severe peritoneal trauma for a period of three hours, the blood pressure shows practically no tendency to fall and sensibility is retained. In contrast, if identical intestinal manipulation is begun more promptly after anesthetization, the blood pressure invariably begins to decline progressively within an hour, has fallen to 60 mm. or below an hour and a half to two hours after opening the abdomen and the animal is in complete shock. An hour's ether anesthesia preliminary to opening the abdomen has proved to be a striking protective against shock, under the conditions of these experiments. If an animal is kept anesthetized for an hour, permitted to recover from the anesthetic, and at once reanesthetized and intestinal manipulation begun, the protective effect of the hour's anesthesia will have disappeared.

IV. Ether has a distinct tendency to hasten the onset of shock once the blood pressure has begun to decline after the abdomen is opened.

V. Cardiac failure is not a factor in the production of shock.

VI. Failure of the vasomotor center is not a primary factor in shock.

VII. The cardio-inhibitory center is shown not only to respond to stimuli but also to function independently during deep shock. Its failure cannot be regarded as a cause of the condition.

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CLINICAL AND ANATOMICAL STUDY OF FIFTY-ONE CASES OF REPEATED CÆSAREAN SECTION WITH ESPECIAL REFERENCE TO THE HEALING OF THE CICATRIX AND TO THE OCCURRENCE OF RUPTURE THROUGH IT

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In 1917 Dr. J. Whitridge Williams published in the Bulletin of The Johns Hopkins Hospital the results of a histological study of 50 uteri removed at Cæsarean section. Included among them were 10 uteri which had been incised at a previous similar operation. They were only briefly described, as Dr. Williams stated that "the details concerning this series will be published in full later." Since that time additional specimens have been added to our collection, and it is my purpose to report the results of a careful clinical and anatomical study of this material.

It is but a natural sequence that, while investigating the histories of the women from whom the uteri were removed, we should likewise consider the closely allied cases in which a conservative Cæsarean section was repeated at a subsequent pregnancy, or delivery was effected through the natural passages. It is only by a careful consideration of such cases that we may be enabled to draw definite conclusions concerning the truth or fallacy of the oft-quoted dictum—"Once a Cæsarean, always a Cæsarean."

Our discussion is based upon the study of 63 pregnancies occurring in 51 women who had previously been subjected to Cæsarean section. Fifty-five of these pregnancies followed a single Cæsarean section, while in eight there were two operations. The manner in which the pregnancies were terminated was as follows:

A second or third Cæsarean section was done in 45 cases.

Vaginal delivery occurred in 17 cases.

Rupture of the old Cæsarean scar occurred in one case.

That the woman who has once been subjected to a Cæsarean section, and who again becomes pregnant, presents an interesting and at the same time a somewhat puzzling problem has been generally recognized and frequently commented upon. Prior to 1876 the mortality following Cæsarean section was appalling, from 50 to 60 per cent of the women dying from infection or hæmorrhage, but at the present day elective Cæsarean section, performed under proper surroundings by men trained to recognize its indications, as well as its contraindications, should be attended by an immediate mortality of not more than one per cent. From an obstetrical point of view we cannot, with fairness, rest content with the immediate results, but must also consider what may happen in the subsequent pregnancies of such women. Rongy has estimated that approximately three per cent of all Cæsarean section scars eventually rupture, and that at least one-half of such accidents terminate fatally. Notwithstanding this very definite menace, and completely ignoring the frequent warnings, which have been sounded by many writers in recent years, surgeons, gynecolo-

gists, and obstetricians throughout the country are performing the operation with increasing frequency.

Proof that the uterine scar constitutes a *locus minoris resistentiæ* in a certain proportion of cases may be obtained by reviewing the literature on rupture of the Cæsarean scar in subsequent pregnancies. Approximately 102 such cases have been reported and summarized by numerous authors. Thus, Wyss, in 1912, analyzed 42 cases, while four years later Bell, Schroeder, and Findley collected 79, 63, and 63 cases, respectively. To the 63 cases reported by the latter, Spalding, in 1917, added 12 others, which he had collected from the literature. Furthermore, Losee reported nine instances of partial or complete rupture in 1918, and since then Davis, DeCourcey, Howson, Freund, Novak, Baisch and Holland have reported additional cases. In addition to the occurrence of actual rupture, a number of cases have been reported in which the uterine scar was so attenuated that rupture would probably have occurred had the uterine distention not been relieved by operation, not to speak of those in which the rupture or extreme thinning of the scar was not recognized, or, if recognized, was not reported.

Naturally, the questions arise: What is the causative factor in the production of the thin, imperfect scar, and what are the conditions predisposing to its rupture? Numerous explanations and theories have been offered which may be roughly classified under the following headings:

1. Infection.
2. Improper suture technique.
3. Unsuitable suture material.
4. Location of the uterine incision.
5. Involvement of the placental site at operation.
6. Implantation of the placenta over the scar, with inversion of fœtal elements.
7. Miscellaneous.

We shall consider each group in some detail.

1. Infection

The important rôle played by infection in the production of an imperfect scar is so generally recognized that a case of rupture or extreme thinning is seldom reported without emphasis being laid upon the presence or absence of fever during the preceding puerperium. Losee asserts that "when infection takes place and the cut surfaces are infiltrated with leukocytes and serum, associated with more or less necrosis, then only that muscle tissue remains which has not become necrotic." The extreme necrosis which may take place in an infected wound is well illustrated by Fig. 1. Findley states that failure to secure perfect healing is partly due to septic infection of the wound, and calls attention to the possible existence of a latent gonorrhœal infection, which "may defeat the most painstaking efforts to secure perfect wound healing." The character of the puerperium was noted in 66 of the 97 cases of rupture studied by Holland, who found that 51 were febrile and 15 afebrile. In commenting upon these figures, he asserts that "infection of the uterine wound may occur without rise of temperature, or with only a very slight one; for example, few will deny that the presence of extensive adhesions to the scar at a subsequent operation is evidence of sepsis during the healing process."

In our opinion the latter part of Holland's statement does not necessarily hold true, and it is permissible to suppose that adhesions may form in the absence of infection, whenever there is a rough, raw surface, such as occurs when the uterine wound has been improperly sutured. For example, in the first case reported in our series the wound had been closed with interrupted silkworm-gut sutures and the stiff knots had been left upon the surface. The puerperium was normal and the scar well-nigh perfect, but nevertheless was covered by dense adhesions. Consequently, if, as is likely, such adhesions resulted from irritation by the stiff knots, it behooves all operators to secure accurate coaptation between the cut edges and to do as little damage as possible to the covering serosa. It must be admitted that imperfect scars may result when the temperature has not been elevated, and in such cases some causative agent other than infection must be sought, while, on the other hand, a scar sufficiently strong to withstand the strain of labor may result even though the record of an elevated temperature indicates that infection had occurred. Here it must be assumed that the infectious process did not involve the uterine incision, or, if it did, that no extensive necrosis resulted.

In the 183 Cæsarean sections, which were done in the service up to the end of December, 1920, there was only one instance of actual rupture of the scar and in this patient the temperature had been elevated for 10 consecutive days following the primary operation. In 15 cases in which the uterus was removed later and studied, and in which we had definite information as to the character of the preceding puerperia, seven were found to be febrile and eight afebrile. In the first group, no trace of the scar could be found in six specimens, while it was only slightly thinned in one. In the second group, the scar could not be located in three instances, while the healing was good in three, fair in one, and poor in one case. Moreover, in three cases the uterus was removed at the third section, so that in such specimens we can only speculate as to which operation had given rise to the scar in question. Of the 13 patients in whom delivery was effected through the natural passages following Cæsarean section, six presented a preceding febrile puerperium.

Such figures, while suggestive, only serve to show how difficult it is to predict the strength or weakness of the Cæsarean scar in the individual case. However, it would seem permissible to infer that the uterine scar will be weak rather than strong if frank infection has occurred in the preceding puerperium, and that such patients should not be subjected to the strain of a prolonged labor, particularly if the original section has been performed on account of pelvic dystocia. On the other hand, when it has been done for some temporary indication, or if there is only moderate pelvic contraction with a small child, even though fever has complicated the former puerperium, we believe that the patient may be allowed to go into subsequent labor, provided that she be kept under careful observation. This view is at variance with that recently expressed by Newell: "It [repeated Cæsarean section] should, however,

be considered obligatory in patients who give a history of a febrile convalescence, since this points to the probability of uterine infection, and it is in these patients that the rupture of the scar in subsequent pregnancies and labors is most to be feared."

2. Suture Technique

Hurried closure of the uterine incision without due care in accurately approximating the cut surfaces, the placing of the sutures too widely apart, and the inclusion of the decidua in the line of sutures may all be factors in producing an imperfect scar. In this clinic the incision is closed with two layers of catgut, the first consisting of deep buried interrupted sutures placed at intervals of about 1 cm., while a superficial running suture brings together the serosal edges. If, after the first layer of sutures has been placed, there is still considerable gaping of the muscularis, an additional continuous buried suture is used. The decidua should be avoided, since any bits of it inverted into the wound may proliferate and develop into areas of unusual friability. Figs. 2 and 3 illustrate the technique.

Fischer, in 1912, directed attention to the danger of suturing the uterus before it has firmly contracted and retracted, and consequently Green, in 1916, advised that the operation should not be undertaken until labor had been in progress for several hours. "It stands to reason," he says, "that the scar will be thicker and stronger if the closing sutures are applied to a uterine wall thickened by several hours of contractions, than when placed in the thin, comparatively flabby wall of a uterus incised before labor has begun." Apparently the rationale of this theory rests upon a mechanical basis; for, if the sutures be laid and tightly tied while the musculature is lax, it is conceivable that when the uterine wall increases in thickness as the result of subsequent contraction, the sutures will either become untied, or else they will tear through the thickened tissue. In the latter event a gap may be left on the inner surface of the uterus, which is invaded by endometrium. Unfortunately, however, it is not always possible to wait for the occurrence of firm contraction, as brisk hæmorrhage may necessitate immediate suturing of the wound. Figs. 4 and 5 illustrate the assumed sequence of events.

Analysis of the operative notes concerning the first operation in our patients, from whom the uterus was removed at a subsequent section and its scar studied microscopically, shows that the character of the uterine contraction was recorded in 11 instances. In eight, firm contraction had occurred before the sutures were placed, and in five of these the scar was normal or could not be found, while in the three others definite thinning was evident. In one of the latter the convalescence was complicated by an outspoken infection, so that it is difficult to determine whether the infection or the slow muscular contraction had played the more important part. On the other hand, in the three instances of poor contraction, there was no trace of the scar in two, while it was very thin in the third case. Moreover, in the one instance in which the old scar ruptured in a subsequent pregnancy, it had been necessary to suture the uterus while its musculature was lax.

It must be admitted that the figures available are too few to permit final conclusions, but they clearly indicate that suture of the uterus after firm contraction has occurred does not necessarily insure an ideal scar.

3. Suture Material

The fact that a wide variety of suture material has been used in closing the uterine incision is sufficient proof that none is entirely satisfactory from every point of view. Plain, formic, and chromicized catgut, silkworm-gut, kangaroo tendon, ordinary black or white silk, metallic wire, etc., have been employed at one time or another. Plain catgut has generally been discarded on account of its rapid absorbability, although Carstens advocates it for that very reason.

In our hands chromic catgut has given relatively satisfactory results. Holland, on the contrary, believes that it is also absorbed more rapidly than is desirable, particularly in the presence of infection.. Upon the analysis of a large number of cases, he found that subsequent rupture occurred two and a half times more frequently after the use of catgut than of silk. Consequently, he is of the opinion that non-absorbable sutures are preferable, and holds that silkworm-gut fulfills the requirements most satisfactorily. Plain silk is a notorious harborer of bacteria, as is admirably illustrated by Case X below. Prusmann objects to non-absorbable sutures on the ground that small channels may be formed about them, and as these may be invaded by bacteria or even by endometrium, necrosis or weakening of the scar may result. Eckstein, in 1904, indicated the advantages of metallic sutures, and suggested the use of thin flat bands of lead, which, in addition to being non-absorbable, would serve as supports for the scar in future pregnancies.

In our series of operations silkworm-gut was used only in a single instance, and the resulting scar was ideal. When the uterus was removed a year later, the sutures were still *in situ* (Fig. 6), but, as has been mentioned previously, dense adhesions had developed along the entire length of the scar, probably as the result of the knots irritating the surrounding tissues. It would seem, therefore, that when this material is used the sutures should be buried, and the superficial muscle layer and peritoneum brought together with catgut over it.

Obviously, the choice of suture material is at present a matter of personal preference, and no definite statement can be made as to which possesses the greatest merit. To my mind, the technique used in laying the sutures is of greater importance than the material of which they are composed.

4. Situation of the Incision

At a Cæsarean section the uterus may be incised in any one of the following four locations; (1) in the midline of the anterior wall; (2) in the posterior wall; (3) in the fundus, either transversely or longitudinally; and (4) in the lower uterine segment, likewise either longitudinally or transversely. In the last group may be included those cases of vaginal hysterotomy, in which the lower uterine segment becomes involved in the incision. Without doubt, in the great majority

of cases the median anterior wall is the site of election, although in recent years there has been a growing tendency to advocate incision of the lower segment. The uterus is opened through the posterior wall only in the rare instances in which its body has undergone extreme forward displacement.

Varying results have been obtained with the several modes of incision and a voluminous literature has accumulated upon the subject. In 1897, Fritsch described his transverse fundal incision, which has been discarded after a number of years of experimentation. Eckstein, in 1904, reported the first case of rupture of a fundal scar in a subsequent pregnancy, and following it numerous similar reports have appeared in the literature. Scheffzek called attention to the fact that in order to secure perfect healing of any wound, its edges should be immobilized, and admitted the impossibility of keeping the actively contracting and relaxing uterus entirely at rest. Furthermore, he pointed out that the fundal incision approached the ideal even less than one through the median wall or the lower uterine segment. In proof of this he reported the findings at autopsy upon a woman who had died from a toxæmia several days after a Cæsarean section, which showed that the sutures in the fundal wound had become loosened or entirely untied, presumably as the result of active uterine contractions. By way of contrast, he also reported his observations upon 10 women who had been subjected to extraperitoneal Cæsarean section. In five of them repeated section was necessary; while of the other five, one was delivered spontaneously, and in four labor was induced in the latter part of pregnancy. In each instance the uterine scar remained intact, although in one the pains continued for 68 hours before delivery was effected. Consequently, he concluded that the scar is much more resistent after extraperitoneal section than after either the fundal or median incision. Spalding holds that "the extraperitoneal Cæsarean section carries with it a better prognosis than the classical abdominal operation." Furthermore, Holland concluded that transverse fundal scars are especially liable to rupture, and Offerman, in 1916, collected 21 such accidents from the literature. In addition to this unusual liability to rupture, he feels that adhesions are especially prone to occur, and that in those cases in which infection of the uterine wound occurs, drainage will be into the abdominal cavity rather than through the abdominal wound, thereby materially decreasing the chances for recovery.

Fischer has described in detail two uteri which had been subjected to previous fundal incisions. In one a complete rupture of the scar occurred in a subsequent pregnancy, while in the other it was so thin that rupture would have undoubtedly occurred had labor not been terminated by operation. From this experience he is convinced that the fundal incision should not be used. Findley has gone even further, and says that "the transverse fundal, extraperitoneal, and cervical incisions have not lessened the liability of rupture in subsequent labors, but on the other hand have probably increased the hazard."

Since our experience with the extraperitoneal and cervical incisions has been limited to four cases, we do not feel qualified to make definite statements concerning their comparative merits. In none of our cases did rupture occur, although in one instance the woman subsequently went through a moderately severe spontaneous labor. Moreover, in two of the uteri which were removed at a subsequent section, examination revealed no trace of the old scar. Rohrbach claims that the scar following the cervical operation practically insures against danger of rupture in future pregnancies, and it is undoubtedly true that only a few instances of this accident have been reported. It must, however, be admitted that this is too favorable a verdict, as Wolff, Franz, Freund and Labhardt have each described cases of rupture. Baisch, in 1920, reviewed the results following 170 Cæsarean sections in the Stuttgart clinic, and attributed the good results to the employment of the transperitoneal cervical operation. Twenty-four of his patients had repeated sections, and in three rupture of the uterus occurred. In the first case it was unquestionably through the old cervical scar; while in the other two he attempts to prove that it was not. In the second case, although the rupture involved the scar, he argues that it had originated in the body of the uterus, as at the first operation the incision had torn upward during extraction of the child so that only a part of it could be covered with the bladder. In the third case the patient had a bicornate uterus in which three pregnancies had occurred. The first was terminated by a transverse fundal incision, the second by a cervical incision, while the third terminated by rupture. On opening the abdominal cavity at that time he found that the cicatrix of the first operation had yielded, while the one in the lower segment was intact. He considers this an excellent demonstration of the superiority of the cervical operation. We, however, cannot agree with his contention; for, even accepting his argument concerning the second case, which appears questionable, he admits one cervical rupture in 24 repeated sections, which is somewhat higher than the 3 per cent incidence following the usual incision.

Before concluding the consideration of the location of the uterine incision, I shall refer to two cases of repeated Cæsarean section which possess points of unusual interest, one reported by Planchu, the other by Harrar. In the former, the three linear scars were plainly visible in the anterior median line at the time the fourth consecutive section was performed. They were equidistant and approximately at the same level and were included in a broad band of thinning—2.5 cm. wide, where the muscle had been replaced in large part by fibrous tissue. An explanation of the mode of production of such a condition is afforded by Harrar's case. Here the uterus had ruptured after a third Cæsarean section, and upon examining the specimen he found that the line of rupture did not involve an old incision but had occurred between two of them. As the distance between the scars was one centimeter, he inferred that a danger zone had been created at the previous operations by cutting the trophic nerves and thereby interfering with the blood supply in that neighborhood. To obviate such a danger he urges that in a repeated Cæsarean section the inci-

sion should be made some distance away from the old scar, or else that the latter should be completely resected.

5. Incision into the Placental Site

Writers upon the subject have advanced two reasons for assuming when the uterine incision involves the placental site that the resulting scar will, in some cases, be thinner than it would have been had the incision been elsewhere. First, as the thickness of the uterine wall at the placental site is several millimeters less than elsewhere, it is argued that the scar will be thinned in like proportion. Second, the fœtal elements may interfere in the healing process. The latter view is held, in a general way, by Spalding, Fischer, and others. However, they, and practically all observers, believe that this is only an accessory factor of no great importance.

For the purpose of determining what relation, if any, incision through the placental site has upon the healing of the uterine wound, I have divided our cases into two groups. The first includes those in which the location of the placenta was noted at the first operation and in which the uterus was removed at a subsequent section and studied histologically; while the second includes patients who were delivered by the natural passages following a preceding section in our clinic. The former group includes 17 specimens, and the latter six cases. In the first group the incision involved the placental site in seven instances, and of these, two uteri showed no trace of the scar, in two there was very slight thinning, while in the remaining three the thinning was quite marked. In the 10 instances in which the placental site was not involved, no trace of the scar was visible in three, it was satisfactory in six, and was poor in one uterus. In the second group the placental site had been incised in two patients, and not in the other four. It may be added that in the single instance of rupture occurring in our series and reported below, the operative note concerning the first section failed to mention the location of the placenta.

From these figures the hasty observer might be led to the conclusion that a definite relation exists between imperfect healing of the scar and the involvement of the placental site at operation. Our observations do not prove it, and in addition it should be remembered that such few figures as are available do not justify binding conclusions. Consequently, we can only say that our findings merely point to the necessity of closer observation of the influence of this factor in the future.

6. Implantation of the Placenta over the Old Scar

Eckstein, in reporting his case of ruptured Cæsarean scar, laid particular emphasis upon the insertion of the placenta over the old scar as a probable cause of the rupture. He assumed that the fœtal elements invaded and weakened the scar, much in the same way as occurs in tubal pregnancy. Spalding states that "while it is plausible that the placental elements might lead to poor healing of the wound in cases where the incision is into the placental site, there is hardly sufficient evidence available to uphold the idea that the syncytium will attack sound scar tissue any more than it will attack sound uterine tissue." Consequently, he believes that the placenta, when inserted over the scar, may even act as a splint and serve to support the weakened uterine wall. At the same time he calls attention to the possibility that the formation of small retroplacental hæmatomata may eventually cause the rupture of the scar as they grow larger. In 1906, Couvelaire reported a series of nine cases of ruptured Cæsarean scar and stated that in five of the six instances in which the placental attachment had been noted, implantation had occurred over the old scar. He therefore concluded that the insertion of the placenta over the scar cannot be considered the sole cause of rupture, but that when it is already thin its invasion by fœtal elements must lead to further thinning and accentuation of its friability.

Our observations concerning the bearing of this factor indicate that it is not important. Strange to say, in each of the three uteri which had been removed after two previous sections the placenta at the third operation was implanted over the old scar. In the first case, both scars were seen and were quite thin; in the second, only one scar was visible and it, likewise, was considerably thinned; while in the third, neither scar was visible. In 17 uteri which had been removed at the second operation, the placenta was implanted over the scar in three. In two of these the scar of the previous section could not be found, while it was well healed in the third uterus. Furthermore, in the one case of rupture the placenta was inserted over the old scar, but in none of these cases was there any evidence that the scar had been invaded by fœtal elements.

7. Miscellaneous

(a) *Excessive Distention of the Uterus.*—In the cases of rupture reported by Woyer, Couvelaire, and Scheffzek, the presence of hydramnios or multiple pregnancy had subjected the uterus to abnormal distention, which was assumed by these authors to have been a predisposing factor. On the other hand, Gilles, in 1916, reported the successful termination of a twin pregnancy without rupture of the uterus, in spite of two previous Cæsarean sections. The combined weight of the two children was 4950 grams.

(b) *Forcible Intrauterine Manipulations.*—Version and extraction, the use of hydrostatic bags, uterine tampons, etc., have been mentioned as possible causes of rupture, although it is only in cases of marked thinning of the scar that such factors are of any importance.

(c) *"Water-Wedge Theory."*—Spalding, in attempting to explain the rupture of the scar in a certain percentage of cases, advanced the theory that a small water-wedge formed by the amniotic sac may serve to dilate the thinned-out scar in exactly the same way that the bag of waters brings about dilatation of the cervix in normal labor.

Before passing on to the consideration of the anatomy of the Cæsarean scar, we shall refer to several investigations concerning its resistance, and then say a few words concerning the incidence of adhesions and their mode of production. In 1910,

Mason and Williams studied the resistance of the Cæsarean scar experimentally. They subjected a number of pregnant animals to Cæsarean section and some time later removed the uterus for investigation. They attached weights to a strip of muscle containing the scar and increased them until rupture occurred, when it was found that it took place through the sound muscle and not through the scar itself. Their experiments gave such uniform results that they drew the conclusion "that a firmly united scar is even stronger than the intact uterine muscle and should easily be able to withstand any strain which the latter is capable of bearing." Moreover, the case reported by Harrar demonstrated that the normal muscle tissue may yield before the cicatrix, although the myometrium in that instance was regarded as having become "devitalized." As anatomical study of the well healed scar shows no reason why it should rupture before the surrounding muscle, it is probable that the statement of Mason and Williams holds true for a "firmly united scar." In the thin, poorly healed wound, on the other hand, there can be little doubt that the rupture occurs directly through the scar and not through the adjacent tissue.

Adhesions

That adhesions are quite common following Cæsarean section is clearly demonstrated by the following observations made in our clinic at repeated operations.

TABLE I

	Adhesions			
	Dense	Filmy	Moderate	No note
After one previous section	17	7	1	4
After two previous sections	6	1	0	0

TABLE II

	Puerperium	
	Febrile	Afebrile
Dense adhesions	8	7
Filmy adhesions	5	3
Moderate adhesions	1	1
No note	2	1

Table II illustrates the fact that while adhesions are more commonly formed after a febrile puerperium, yet the absence of fever does not necessarily mean that adhesions have not formed.

It is difficult to determine just how much harm such adhesions do. Doubtless, they may give rise to considerable abdominal discomfort, which may occasionally be so great as to necessitate a second operation; and Humpstone reports an instance in which it was necessary to remove the uterus before the symptoms disappeared. In other patients the adhesions may be so dense that the subsequent operation is performed under tremendous difficulties, and in rare instances regrettable accidents, such as injury to the gut or bladder, can be directly traced to their presence. For example, in Case XIX described below, after the adhesions had been freed, the anterior surface of the uterus presented such an extensive raw bleeding area that hysterectomy was necessary.

Can the formation of adhesions be prevented? Davis has suggested that the liability toward their development may be lessened by resorting to the high abdominal incision. This, however, is a mere supposition, and inasmuch as the advantages of the lower incision are so great, we do not feel that it should be discarded in favor of the higher one. Consequently, it seems that the only way at present by which we can lessen the incidence of adhesions in the absence of infection is by securing as perfect coaptation between the cut surfaces as possible, thereby leaving a minimal area which can excite mechanical irritation.

Anatomy of the Cæsarean Section Scar

For convenience in description Cæsarean scars may be divided into two main groups: first, those which have ruptured or were on the point of rupturing when the abdomen was opened; second, those in which satisfactory union has persisted.

As Losee and also Couvelaire have pointed out, the first step in the mechanical healing of the uterine scar is the deposition of fibrin between the edges of the wound, which acts as a framework for the ingrowing tissue which will eventually determine the character of the cicatrix. In spite of the constant contraction and relaxation of the uterus, if infection is absent, and the sutures have been so laid that the edges of the incision remain approximated, firm union will almost invariably result. On the other hand, if there is necrosis due to infection, or if the sutures tear through, leaving a gaping wound, there is an ingrowth of endometrium, which may involve almost the entire thickness of the wound. Such a scar, when seen in a subsequent pregnancy, is made up almost entirely of decidua and peritoneum, and its gross appearance in the unopened distended uterus is characteristic. Instead of the vertical shallow depression seen in the more perfectly healed scars, it is represented by a glistening translucent band of tissue which bulges outward beyond the general surface; while after the uterus has been emptied, hardened, and cut in cross-section, the scar is marked by very deep depressions on both the outer and inner surfaces of the uterus. On microscopical examination it will be found that it is composed almost entirely of thickened and highly vascularized serosa overlying the decidua. There is an increase in the fibrous tissue and a definite decrease in the elastic fibres, while occasionally a few muscle fibres may be present.

Between a scar of this nature and one which has healed perfectly all gradations may be observed in so far as gross appearance and thickness are concerned. Nor is the microscopical picture markedly different in the thin scar as con-

trasted with the well healed one, except when there has been no muscular union. Figs. 7, 8 and 10 depict the characteristic appearance of well healed scars, while Fig. 9 (A) shows a scar which is considerably thinner than the other three. In all there is a slight depression both upon the inner and outer surfaces of the uterus, while the cicatrix itself appears as a white line joining the two depressions. Unless such scars are examined under the microscope, one is apt to infer that they are made up of fibrous tissue alone. Such, however, is not the case, and in all four specimens muscle fibres can be seen running directly across the old line of incision, with no break in their continuity and with only slight distortion of their course.

Jolly and others have reported instances of partial rupture of the old Cæsarean scar. Upon studying such specimens in detail, they found that one portion of the scar was composed solely of decidua and peritoneum, while the rest was made up of normal muscle. Similar variations in thickness throughout the length of the same scar are well illustrated by Figs. 15 and 16, which are photographs from the two sides of a block one centimeter thick, and show that within so short a distance the thickness of the scar may be doubled.

Briefly then, Cæsarean section scars vary considerably in thickness, depending upon the accuracy with which the margins of the wound have been brought into apposition. Under ideal conditions the muscle unites perfectly, and its fibres cross the site of the incision as if it had never been made. When, however, there has been no muscle union, the scar is made up solely of decidua and peritoneum. Most scars are marked by funnel-shaped depressions on the outer and inner surfaces of the uterus. The muscle bundles are not much distorted, the formation of fibrous tissue is much less than would be anticipated, and when it is increased, the elastic fibres are correspondingly diminished in number. (See Fig. 7.)

Fig. 7, which represents a low power microscopic picture, gives an idea of the characteristic conditions obtaining in a well healed wound, while the photographs accompanying some of the case reports clearly depict some of the gross variations which may be encountered.

In the case reports which immediately follow, we shall describe the gross appearance and microscopic structure of the Cæsarean scar as it appeared in 21 uteri which were removed at a second or third section, and which will serve to amplify and reinforce what has already been said.

CASE REPORTS AND DESCRIPTION OF SPECIMENS

In the following cases the uterus was either removed at operation or secured at autopsy. A brief clinical synopsis precedes the more detailed description of the specimen.

CASE I.—House No. 1274, 24 years, black. Generally contracted rhachitic pelvis, D. C. 10.5 cm.

Three vaginal deliveries. Fourth labor ended by Cæsarean section after a second stage of three hours. Child dead—4180 gm. Incision through the placental site; closure with interrupted silkworm-gut sutures. Puerperium normal except for a rise of temperature to 100.4° on the second day. Fifth labor ended by Cæsarean section followed by supravaginal amputation of the uterus. Uneventful recovery. Omental adhesions, placenta on posterior wall. No note as to the condition of the cicatrix before the incision of the uterus.

Description of Specimen.—After hardening, the uterus measures 14 x 12 x 10 cm. On the midline of its anterior surface is a mass of adhesions, evidently over the scar of the previous operation. On removing them, a linear depression 8 cm. long becomes visible, with the silkworm-gut sutures still in place. (Fig. 6.) On cross-section through the uterus the scar is represented by depressions on its inner and outer surfaces, which are joined by an irregular whitish line (Fig. 8). The uterine wall is 11 mm. thick at the site of the scar, as compared with 17 mm. adjacent to it, a ratio of 1 to 1.54. On microscopical examination no trace of the scar is seen except for the funnel-shaped depressions and a slight irregularity in the arrangement of the muscle fibers. The external depression is filled with highly vascularized connective tissue, while the inner one is lined with decidua containing many glands. In the center of the scar is a small island of characteristic decidual tissue. The Weigert stain shows a decrease in the elastic tissue at the site of the scar.

CASE II.—House No. 7145, 27 years, black. Generally contracted rhachitic pelvis, D. C. 8.75 cm.

First labor, spontaneous, premature; second, pubiotomy. The third and fourth pregnancies were ended by Cæsarean section with silk sutures. Ideal recovery after both operations except for a mastitis in the fourth puerperium. The placenta was on the posterior wall in the first, and on the anterior wall in the second section. The fifth pregnancy ended in a 3 months' abortion, and the sixth was terminated by a Porro section. Puerperium normal except for a mastitis. There were dense adhesions between the uterus and anterior abdominal wall, but no traces of the cicatrices of the previous Cæsarean sections were visible. The placenta lay anteriorly.

Description of Specimen.—After hardening, the uterus measures 10 x 11 x 8 cm. Numerous dense adhesions are present over its anterior surface. On either side of the present incision is a vertical depression apparently corresponding to the scars of the previous operations. On cross-section, the scars are clearly visible and are represented by the typical funnel-shaped depressions on the outer and inner walls (Fig. 9). The scar on the left is 6 mm. thick, while the adjacent uterine wall is 23 mm., a ratio of 1 to 4. On the right side the scar is 11 mm. thick, a ratio of 1 to 2. On microscopical examination, except for the thinning of the uterine wall, there is little to indicate the location of the former incisions. There is no scar tissue and the muscle fibers run directly across from side to side. The inner depressions are lined with decidua, while the outer ones are filled with thickened scar-like peritoneum. The elastic fibers are decreased. It is impossible to say which scar belongs to the first and which to the second operation. One is almost twice as thick as the other, and the only factor noted at either operation that might have influenced the healing was the poor contraction of the uterus at the first section.

CASE III.—House No. 6540, 22 years, black. Generally contracted rhachitic pelvis, D. C. 9.5 cm.

The first pregnancy ended by a conservative Cæsarean section. The placenta lay posteriorly, the uterus contracted firmly, and the incision was closed with catgut. The puerperium was febrile for five days. The second labor was spontaneous premature at seven months. The third pregnancy was terminated by a Porro section, the operation being performed 19 hours after the onset of labor. There were several dense adhesions between the uterus and the anterior abdominal wall; the placenta was inserted posteriorly; the puerperium was normal. The scar of the previous section was not noted at the time of the operation.

Description of Specimen.—After hardening, the uterus measures 17 x 12 x 9 cm. The posterior surface is free except for a few velamentous adhesions. On its anterior surface the scar of the previous operation is indicated by a deep depression, from the lower angle of which a broad adhesion extends down to the free peritoneal margin. On cross-section (Fig. 10), the scar is represented by funnel-shaped

depressions on both the outer and inner surfaces of the uterus. Joining them is a white puckered line resembling scar tissue. The uterine wall measures 28 mm. in thickness, while the scar is 22 mm. thick, a ratio of 1 to 1.36. On microscopical examination the only trace of scar consists in a slight irregularity in the arrangement of the muscle fibers and some increase in the fibrous tissue. The elastic tissue is decreased.

Case IV.—House No. 6847, 24 years, black. Generally contracted rhachitic pelvic, D. C. 9.25 cm.

First pregnancy ended by a conservative Cæsarean section. The placental site was incised, the uterus contracted firmly, and closure was with catgut. Puerperium uncomplicated.

Second pregnancy ended by a Porro section. Two broad adhesions attached the anterior surface of the uterus to the abdominal wall. The placenta lay posteriorly. No sign of the old uterine scar. Puerperium normal.

Description of Specimen.—After hardening, the uterus measures 19 x 13 x 10 cm. Two broad bands of adhesions on the anterior surface. Careful examination, grossly and microscopically, shows no trace of the old scar.

Case V.—House No. 6939, 18 years, black. Generally contracted rhachitic pelvis, D. C. 10.25 cm.

First pregnancy ended by a conservative Cæsarean section. Placental site not incised; closure with catgut. The character of the uterine contraction not recorded. The puerperium was complicated by wound infection, the temperature being elevated for 15 days. The second pregnancy was terminated by a Porro Cæsarean section. In attempts to extract the child through too small an incision, the uterus was torn down to the bladder and into the right broad ligament, necessitating its removal. The placenta was inserted posteriorly. The puerperium was normal except for a simple mastitis.

Description of Specimen.—After hardening, the uterus measures 15 x 12 x 10 cm. The surfaces are free from adhesions and there is no trace of the old scar.

Case VI.—House No. 6076, 23 years, white. Generally contracted rhachitic pelvis, D. C. 10 cm.

The history of the first two labors is meagre. Both were instrumental and both children were stillborn. The third labor was terminated by a conservative Cæsarean section. The placental site was not involved, the uterine contraction was poor and closure was with catgut. Puerperium febrile for six days. Fourth labor ended by a Porro section. There were a few filmy adhesions on the anterior surface of the uterus. The placenta lay posteriorly. Puerperium normal.

Description of Specimen.—After hardening, the uterus measures 14 x 14 x 8 cm. A few thin adhesions cover its anterior surface, in the midline of which is a smooth shallow depression indicating the site of the previous operation. On cross-section, except for this depression and a similar one on the inner surface, there is no trace of the scar. The uterine wall measures 26 mm. in thickness, the scar 23 mm., a ratio of 1 to 1.13. Microscopically there is no sign of scar tissue, and the muscle bundles show complete regeneration.

Case VII.—House No. 8087, 29 years, black. Generally contracted rhachitic pelvis, D. C. 8.5 cm.

The first and second labors were ended by a conservative Cæsarean section and a destructive operation, respectively, both operations being performed elsewhere. The third pregnancy was terminated by a Porro section. Several loops of gut were densely adherent to the anterior abdominal wall and anterior surface of the uterus. The placenta was inserted posteriorly. Puerperium normal.

Description of Specimen.—After hardening, the uterus measures 15 x 16 x 7 cm. On the anterior surface is a depressed raw area, representing that portion which was covered by adhesions, the latter overlying the scar of the previous operation. On cross-section, the scar is represented by shallow depressions on the outer and inner surfaces of the uterus. The thickness of the scar is 19 mm., that of the adjacent wall, 25 mm., a ratio of 1 to 1.3. Microscopically, the inner depression is seen to be filled with decidua, while the outer is lined with vascular serosa. The muscle fibers run directly across the line of the former incision without break in continuity. There is no increase in fibrous tissue.

Case VIII.—House No. 8137, 31 years, black. Generally contracted rhachitic pelvis, D. C. 9.5 cm.

The first pregnancy was terminated by a conservative Cæsarean section. The placental site was incised, the uterus contracted firmly; closure with catgut. Puerperium normal. Second labor ended by a destructive operation elsewhere. Third labor ended by a Porro section. There were a few thin omental adhesions on the anterior surface of the uterus, but no sign of the previous scar. Placenta inserted posteriorly. Puerperium normal.

Description of Specimen.—After hardening, the uterus measures 16 x 14 x 6.5 cm. Upon the anterior wall, half a centimeter lateral from the present incision is a slight vertical depression, 2 mm. deep, and 4 cm. in length. On cross-section, the usual funnel-shaped depressions are seen on the outer and inner surfaces. The scar measures 18 mm. in thickness, the adjacent uterine wall, 22 mm., a ratio of 1 to 12. Microscopically, no trace of the scar can be found except for the depressions just mentioned. There is no increase in fibrous tissue.

Case IX.—House No. 8332, 21 years, black. Generally contracted rhachitic pelvis, D. C. 9.5 cm.

The first pregnancy was terminated by a conservative Cæsarean section. The site of the placental attachment was not recorded; uterine contraction poor; closure with catgut. Puerperium normal. A conservative Cæsarean section ended the second pregnancy. There were numerous filmy adhesions near the fundus, while lower down was a single broad adhesion running to the old abdominal scar. The placental site was incised, the uterus contracted firmly, and closure was with catgut. The scar of the previous operation was not visible. The puerperium was complicated by infection. The abdominal wound broke down on the sixth day, and a sinus developed which extended well down into the uterus. A pelvic abscess was opened and drained through the vagina on the seventeenth day. The third pregnancy was terminated by a Porro section. Dense adhesions covered the entire anterior surface of the uterus. The placenta lay anteriorly. Puerperium normal.

Description of Specimen.—After hardening, the uterus measures 15 x 13 x 6 cm. The present incision lies to the left of the midline. The entire anterior surface presents a ragged appearance due to adhesions. In the midline the scar of one of the previous operations is marked by a slight depression. On cross-section there is a similar, though much deeper, depression on the inner surface, but there is no trace of a second scar. The scar is 20 mm. in thickness; of this, 4 mm. is made up of fibrous peritoneal tissue, 4 mm. of muscle, and 12 mm. of a triangular wedge of decidua. The adjacent uterine wall measures 22 mm. On microscopical examination it is seen that, although there has been some muscle reunion, the individual bundles are greatly distorted, with a marked increase in the fibrous tissue in its locality. Presumably this scar is the result of the second operation.

Case X.—House No. 8679, 24 years, black. Generally contracted rhachitic pelvis, D. C. 10.25 cm.

The first pregnancy was terminated by a conservative Cæsarean section elsewhere. Three years later the patient was admitted to the surgical service of this hospital with the following history: Fifteen months after the Cæsarean section the abdominal wound began to drain, the discharge consisting mainly of blood, but occasionally containing pus. A sinus tract, which extended down into the uterine cavity, was dissected out, and a number of heavy black silk sutures were removed from the uterine wall. Recovery was uneventful. Sixteen months later the second pregnancy was terminated by a Porro section. A few thin omental adhesions were attached to the anterior

surface of the uterus. Placenta posterior. Puerperium normal except for a simple mastitis.

Description of Specimen.—After hardening, the uterus measures 13 x 10 x 7 cm. To the left of the present incision is a slightly depressed area 2 mm. wide, and 7 cm. long, which apparently represents the old scar. On cross-section, however, there is no depression on the inner surface of the uterus, and microscopically no trace of the scar can be found.

CASE XI.—House No. 8826, 24 years, black. Generally contracted rhachitic pelvis, D. C. 9.75 cm.

The first labor ended spontaneously after 30 hours, the child being stillborn. The second pregnancy was terminated by a conservative Cæsarean section. The placental site was incised, the character of the uterine contraction was not recorded; closure with catgut. Temperature elevated to 101.4° on the second day. The third pregnancy was also ended by a conservative Cæsarean section. Several loops of small intestine were adherent to the abdominal scar and one of them was accidentally opened. It was repaired at once with silk. The omentum was adherent to the fundus. The placental site was incised, the character of the uterine contraction was not recorded; closure with catgut. Puerperium normal. The fourth labor was terminated by a third Cæsarean section and sterilization effected by resection of the tubes. Again an adherent loop of gut was opened, and was repaired with silk. A few omental adhesions covered the fundus. The placental site was incised, the uterus contracted well; closure with catgut.

On the third day of the puerperium the abdominal wound broke down, exposing the anterior surface of the uterus. This was covered with small glistening blebs filled with gas. A drain was inserted and the wound closed with silkworm-gut. Cultures of the wound showed *B. aërogenes capsulatus, B. coli, Staphylococcus aureus,* and *streptococci.* The patient died 12 hours later and autopsy showed a generalized peritonitis (gas bacillus); hæmorrhage from the uterine incision; diphtheritic colitis; epithelial necrosis of the kidneys.

Description of Specimen.—After hardening, the uterus measures 17 x 12 x 6 cm. On the anterior surface is a depressed area, more or less covered by fine adhesions, corresponding to the partially broken down wound of the recent operation. Several of the catgut sutures have become untied, and for a distance of 2 cm. at the upper angle of the incision there has been complete separation of its edges. On cross-section (Fig. 11), it is seen that the cut surfaces are covered by necrotic tissue and at no place is there any sign of firm union. The scars of the previous operations are not visible. Microscopical examination shows that the decidua has been replaced, in large part, by fibrin, leucocytes, and necrotic tissue. The musculature presents a peculiar areolated appearance due to the formation of gas pockets. In many places the individual muscle cells are undergoing degeneration. There is no evidence of beginning muscular union.

CASE XII.—House No. 9115, 19 years, black. Pelvis normal.

The first pregnacy was terminated elsewhere by a Cæsarean section, the indication being "convulsions." The patient was admitted to this hospital in the eighth month of her second pregnancy. Blood pressure 180; the urine contained 3 gm. of albumin per liter. Labor was induced by means of a bougie. After pains had lasted for 12 hours, the patient had her first convulsion, followed in a few minutes by a second. As the cervix was still undilated and the child dead, it was decided to remove the uterus unopened. The omentum was adherent to the anterior surface of the uterus. Puerperium febrile.

Description of Specimen.—After hardening, the uterus measures 22 x 16 x 13 cm. On the anterior surface are a few thin adhesions. No trace of the old scar. On cross-section the placenta is found to lie anteriorly. There is no sign of the usual depressions which so frequently represent the line of former incision. Microscopical examination shows no increase in fibrous tissue. The Weigert stain shows the presence of large numbers of streptococci in the decidua, thus demonstrating the wisdom of removing the uterus, rather than being content with a conservative operation.

CASE XIII.—House No. 9323, 33 years, black. Generally contracted rhachitic pelvis, D. C. 9 cm.

The first pregnancy ended in a spontaneous abortion at the third month, the second in a conservative Cæsarean section. The placenta lay posteriorly; character of the uterine contractions not recorded; closure with catgut. The puerperium was febrile for the first three days. The third pregnancy was terminated by a Porro section, the vulva being so completely covered by a foul, sloughing mass of condylomata that a conservative operation would have almost certainly been attended by infection. There were no adhesions, and the placenta lay beneath the old scar. Puerperium normal.

Description of Specimen.—After hardening, the uterus measures 15 x 11 x 6 cm. Extending from the fundus downward for a distance of 10 cm., and with its lower half slightly to the right of the present incision, is a vertical depression, representing the scar of the previous operation. It averages 1.5 cm. in width, and its deepest portion lies 0.5 cm. beneath the general surface (Fig. 11). It presents a number of transverse depressions, which are apparently due to the individual sutures. On cross-section (Fig. 12) the scar is marked by typical depressions on both surfaces, whose tips are 16 mm. apart, as compared with 25 mm. in the adjacent uterine wall, a ratio of 1 to 1.59. On microscopical examination there is considerable distortion of the individual muscle bundles, although they definitely run from side to side without break. There is no increase in the fibrous tissue.

CASE XIV.—House No. 9539, 24 years, black. Generally contracted rhachitic pelvis, D. C. 8 cm.

First pregnancy terminated by conservative Cæsarean section elsewhere. She was admitted in her second pregnancy, after having been in labor for 30 hours with numerous vaginal examinations. A Porro section was done with difficulty on account of dense adhesions between the lower angle of the abdominal scar and the anterior surface of the uterus. The scar of the previous Cæsarean was not visible before the uterus was opened. The placenta lay posteriorly. Puerperium febrile.

Description of Specimen.—After hardening, the uterus measures 15 x 12 x 8 cm. Externally the scar is represented by a very slight depression along the upper third of the anterior wall. On cross-section (Fig. 13) the uterine cavity presents a triangular appearance, the base being formed by the posterior wall and the apex by the funnel-shaped depression on the inner surface of the anterior wall. Upon microscopical examination no trace of scar tissue can be found and the muscle fibers at the site of the scar are only very slightly disarranged.

CASE XV.—House No. 9530, 31 years, white. Simple flat pelvis, D. C. 10.75 cm.

In the first pregnancy the child was delivered by pubiotomy after a second stage of 14 hours, the D. C. at that time measuring 9.75 cm. The second pregnancy was terminated by a conservative Cæsarean section with an uneventful recovery. Incision into the placental site; character of uterine contraction not recorded; closure with catgut. The third pregnancy was ended by supravaginal amputation of the uterus. There were several large adhesions extending from the old abdominal scar to the anterior surface of the uterus. Placenta posterior; puerperium normal.

Description of Specimen.—After hardening, the uterus measures 17 x 13 x 7 cm. There was no trace of the old Cæsarean scar either on gross or on microscopical examination.

CASE XVI.—House No. 10243, 21 years, black. Flat rhachitic pelvis, D. C. 10 cm.

First pregnancy terminated by a conservative Cæsarean section. The placenta lay posteriorly; character of the uterine contractions not recorded; closure with catgut. Puerperium febrile for two days. In her second pregnancy the patient was admitted to the hospital after having been in labor 15 hours with numerous vaginal examinations. Cæsarean section with supravaginal amputation of the uterus, followed

by a febrile puerperium for five days. The placenta was posterior. There was a single broad adhesion attaching the omentum to the anterior surface of the uterus.

Description of Specimen.—After hardening, the uterus measures 14 x 11 x 7 cm. In its contracted condition a number of transverse markings are visible on the anterior surface, apparently corresponding with the sutures of the former operation. On cross-section there is no trace of the scar, except immediately adjoining the uterine cavity where there is an infolding, 7 cm. in length, perhaps indicating that union had been faulty in that location. Microscopical examination shows no trace of scar tissue.

Case XVII.—House No. 10792, 28 years, black. Generally contracted rhachitic pelvis, D. C. 9 cm.

The first two pregnancies were terminated by Cæsarean sections, the first being performed elsewhere. At the second the uterus was found loosely adherent to the anterior abdominal wall. The placenta was inserted on the anterior wall; the uterus contracted slowly, and closure was with catgut. Puerperium febrile for seven days. The third pregnancy was ended by a Porro section. Broad adhesions extended from the abdominal wall to the anterior surface of the uterus. Placenta posterior; puerperium normal.

Description of Specimen.—After hardening, the uterus measures 16 x 11 x 5.5 cm. The entire anterior surface presents a raw surface which was covered by adhesions at the time of operation. A single scar is visible as a slight linear depression not more than 1 mm. in depth on the external surface, while on the inner surface there is a deeper depression, 7 cm. in length (Fig. 14). Cross-sections made at various levels reveal considerable variation in the thickness of the scar (Figs. 15 and 16). On microscopical examination there is a slight increase in the fibrous tissue, but the musculature has regenerated completely and there is no distortion of the individual fibers.

Case XVIII.—House No. 10808, 25 years, black. Generally contracted rhachitic pelvis, D. C. 10.5 cm.

First pregnancy ended by an extraperitoneal Cæsarean section, after 24 hours of labor. Incision closed with catgut. There was a wound infection and the puerperium was febrile for six days. Second pregnancy terminated by a conservative Cæsarean section. Placenta posterior; uterine contraction fair; closure with catgut. The puerperium was febrile for seven days. The third pregnancy was ended by a Porro section. There were dense adhesions between the abdominal wall and uterus and also about the site of the extraperitoneal section. The placenta lay posteriorly; puerperium normal.

Description of Specimen.—After hardening, the uterus measures 15 x 12 x 9 cm. To the left of the present incision is the scar of the second operation. It is marked by a shallow depression on the outer surface and a much deeper one on the inner surface. The scar measures 25 mm. as compared with a thickness of 35 mm. in the adjacent uterine wall, a ratio of 1 to 1.4. On microscopical examination there is complete regeneration of the musculature at the site of the scar, but there is also a considerable increase in the fibrous tissue. There is no trace of the scar of the extraperitoneal operation.

Case XIX.—House No. 10758, 26 years, black. Generally contracted rhachitic pelvis, D. C. 10 cm.

First pregnancy terminated by a conservative Cæsarean section elsewhere. The patient was in bed with a discharging wound for two months following it. At the second section done at the onset of labor, the lower two-thirds of the uterus was broadly adherent to the old abdominal scar, and after the adhesions had been released such an extensive raw bleeding area was left that it was thought best to remove the uterus. The placenta was inserted on the posterior wall; puerperium normal.

Description of Specimen.—After hardening, the uterus measures 15 x 12 x 6 cm. On the anterior surface is the ragged area referred to above. On cross-section, the scar of the previous operation is visible as an irregular whitish line joining funnel-shaped depressions on the outer and inner surfaces (Fig. 17). On microscopical examination there is little to mark the line of any former incision, the muscle fibers running from side to side without break in continuity and with only very slight increase in the fibrous tissue.

Case XX.—House No. 11047, 19 years, black. Generally contracted rhachitic pelvis, D. C. 8.75 cm.

The first pregnancy was ended by a conservative Cæsarean section at the onset of labor. The placental site was incised, the uterus contracted firmly, and closure was with catgut. Puerperium normal except for a rise of temperature to 101° on the second day. In second pregnancy the patient was admitted 36 hours after the onset of labor with intrapartum infection. A Porro section was performed with eventual recovery after a stormy convalescence. Dense adhesions bound the anterior surface of the uterus to the abdominal wall. Placenta posterior.

Description of Specimen.—After hardening, the uterus measures 15 x 12 x 8.5 cm. In the midline is a slight longitudinal depression which corresponds with the scar of the previous operation. Cross-sections show almost perfect healing. The thickness of the scar is 21 mm., that of the adjacent uterine wall 29 mm., a ratio of 1 to 1.4. Microscopical examination shows normal muscle running directly across the line of former incision, with no increase in fibrous tissue.

Ruptured Cæsarean Scar

The following is the clinical history and the description of the amputated uterus from the single instance in our series in which the scar of a previous Cæsarean section ruptured. Figs. 18 and 19 show the anterior surface and cross-section of the uterus.

Case XXI.—House No. 7570, 24 years, black. Generally contracted rhachitic pelvis, D. C. 9.5 cm.

The first pregnancy was terminated by a prolonged spontaneous premature labor. The second was ended by a Cæsarean section, seven hours after the onset of labor. The uterus retracted poorly, and the incision was closed with two layers of chromic catgut. The puerperium was febrile for 10 days.

The third pregnancy progressed normally to the seventh month. On November 29, 1915, the patient complained of much abdominal pain, and was seen in her home by the out-patient service. As she was not in labor, and as the result of the examination was unsatisfactory, she was instructed to report to the dispensary on the following afternoon. This she did, walking a distance of six or eight blocks each way. She returned the next day with slight vaginal bleeding and was admitted to the hospital. On examination the cervix admitted one finger easily, while just above the internal os is a firm, rounded tumor apparently projected from the posterior wall of the uterus into its cavity, so that a tentative diagnosis of myoma was made. The abdomen was slightly distended but not sensitive, and it was impossible to map out the fœtus or to hear the fœtal heart. Temperature normal, pulse 100.

Under the supposition that we had to deal with a myoma, which would interfere with the birth of the dead child, laparotomy was decided upon. When the abdomen was opened with a median incision, a small amount of bloody fluid escaped and the dead fœtus surrounded by the placenta and membranes lay free in the abdominal cavity. The uterus was tightly contracted, with a large, jagged, irregular, blood-stained opening occupying its anterior wall. There was no bleeding, and what had appeared to be a myoma on vaginal examination was found to be the firmly contracted posterior wall of the uterus. The organ was then removed by supravaginal amputation, and the patient made an ideal recovery.

The interesting points in connection with the case are:

(a) the impossibility of determining when the rupture occurred;
(b) the trifling clinical signs connected with it;
(c) the difficulty of diagnosis;
(d) the absence of serious hæmorrhage, and
(e) the total absence of shock both before and after the operation.

Description of Specimen.—The uterus, after hardening, measures 10x8x6 cm. On its anterior surface, just to the left of the midline, is a jagged, irregular blood-stained opening 6 cm. in length. There are practically no adhesions. Upon cross-section, it is seen that the muscle had failed to unite after the first section, as is shown by the fact that the edges of the opening are smooth and show no sign of recent tear. Evidently the scar had been composed only of decidua and peritoneum, which had yielded when the uterine distention had become pronounced. Microscopical examination bears out this supposition, as the decidua is found to cover the entire inner surface of the rupture, and to extend up to the peritoneum, which is quite thick and scar-like. Nowhere is there any suggestion that muscle union had occurred. The placenta had been implanted anteriorly over the scar.

Unfortunately, in a small number of our repeated Cæsarean sections, which were followed by removal of the uterus, the specimen was lost or mislabeled. Likewise, in a number of instances the patient was sterilized at the subsequent section by resection of the Fallopian tubes, and consequently anatomical studies of the scar could not be made. The main interest in such cases lies in the fact that they serve to demonstrate that the uterine scar was able to withstand the strain incident to a second or third pregnancy. Tables III and IV have been so arranged as to give the salient points in each case without making a detailed report necessary.

Delivery by the Natural Passages, Following Cæsarean Section

In 1904, Von Leuwen was able to find in the literature 32 instances in which a previous Cæsarean section had been followed by delivery through the natural passages, and since then Brodhead, J. T. Williams, Willson, Harrar, Davis, Breitstein, Mason, Humpstone and others have reported similar cases. Study of their material shows that pelvic dystocia had only occasionally afforded the indication for the original operation, but that it had generally been undertaken for some such temporary complication as eclampsia or placenta praevia. Naturally, this is what one would expect, for had the pelvic contrac-

TABLE III

Outline of the Clinical History of Patients Whose Uterus Was Lost, or of Patients Sterilized at Second Section by Resection of the Fallopian Tubes

Case number	First operation					Second operation			Remarks
	Indication	Placental site	Closure	Uterine contraction	Puerperium	Placental site	Adhesions	Puerperium	
1520	Pelvic dystocia.	Posterior.	Deep silk superficial catgut.	Not recorded.	Febrile.	Not recorded.	Moderate.	Febrile.	Uterus removed but lost. No record of scar.
1548	"	Anterior.	Deep silk superficial catgut.	Not recorded.	"	Anterior.	Not recorded.	.....	Excessive bleeding. Patient died on table.
1611	"	Posterior.	Catgut.	Firm.	"	Anterior.	Dense.	Febrile.	Death on 8th day, infection. Uterus secured at autopsy but lost.
5152	"	.....	.....	.....	.....	Posterior.	"	Afebrile.	First operation in Pittsburgh. No admissions after 2d section.
6787	"	Anterior.	Catgut.	Not recorded.	Febrile.	"	"	Febrile.	No subsequent admissions. No note of scar.
8242	"	Not recorded.	"	Not recorded.	Afebrile.	"	Moderate.	Afebrile.	Tubal sterilization. Old scar not seen.
8303	"	Anterior.	"	Firm.	"	"	Dense.	"	Tubal sterilization. No mention of old scar.
8597	"	Anterior.	"	Not recorded.	"	Anterior.	Not recorded.	"	Tubal sterilization. No mention of old scar.
8666	"	Posterior.	"	Poor.	"	Posterior	Filmy.	"	Tubal sterilization. Old scar not seen.
9169	"	.....	"	.....	Febrile.	"	Filmy.	"	First operation extraperitoneal. No subsequent admissions.
9222	"	.....	.....	.....	.....	"	Not recorded.	"	First operation done elsewhere. Tubal sterilization. Old scar-depressed line 5 cm. long.
9547	"	Posterior.	Catgut.	Not recorded.	Afebrile.	"	Filmy	Febrile.	No subsequent admissions. Old scar not seen.
10120	"	.....	.....	.....	.....	"	Dense.	Afebrile.	First operation in Washington, D. C. No subsequent admissions. Old scar not seen.
10212	"	Posterior.	Catgut.	Poor.	Febrile.	"	Filmy.	Afebrile.	No subsequent admissions. Old scar not seen.
10379	"	Anterior.	"	Good.	Febrile.	"	Dense.	Febrile.	No subsequent admissions. Old scar visible as thin depressed line.
10631	"	Posterior.	"	Poor.	Afebrile.	Anterior.	Dense.	Afebrile.	No subsequent admissions. Old scar not seen.

TABLE IV

Outline of Two Cases in Which Two Cæsarean Sections Preceded the One in Which Tubal Sterilization Was Effected

Case number	First operation					Second operation					Third operation			Remarks
	Indication	Placental site	Closure	Uterine contraction	Puerperium	Placental site	Uterine contraction	Closure	Adhesions	Puerperium	Placental site	Adhesions	Puerperium	
8955	Pelvic dystocia.	.....	.....	.....	.....	Anterior.	Firm.	Catgut.	Dense.	Afebrile.	Posterior.	Filmy.	Afebrile.	First operation elsewhere—extraperitoneal. Tubal sterilization.
9254	Pelvic dystocia.	Anterior.	Catgut.	Not recorded.	Febrile.	Posterior.	Not recorded.	Catgut.	Filmy.	Febrile.	Anterior.	Dense.	Febrile.	Tubal sterilization. One of old scars visible as depressed line.

tion been sufficiently pronounced to demand a Cæsarean section at the first labor, those subsequent to it would not be likely to terminate spontaneously. Occasionally, however, even in such cases, the patient may not realize the gravity of her condition, and may fail to summon medical aid until labor has been in progress for a number of hours, when examination may show that the head has become sufficiently molded to permit its descent into the pelvis, and the labor may terminate spontaneously, or at most by a simple forceps delivery. Doubtless had most of these women been seen before the onset of labor, they would have been subjected to a repeated section, for in the presence of a definite degree of disproportion we should not allow a vigorous test of labor, although, as has already been pointed out, if the disproportion is slight, we may allow labor to progress under careful observation.

The points of interest in our 13 cases of delivery by the natural passages following a Cæsarean section are outlined in Table V. It will be noted that in 11 there was a varying degree of pelvic contraction, although in three it had not been sufficiently pronounced to furnish the indication for the previous section. Moreover, in Cases 5959, 6927, and 8572 the child was so premature that the question of pelvic dystocia did not enter into consideration at the subsequent labor. They are of interest, however, from the fact that active labor pains persisted for 18, 15, 7.75 hours, respectively, and thus adduced additional proof of the ability of the well healed scar to withstand the strain of a moderately severe labor.

As 48 of our patients were subjected to one or more repeated Cæsarean sections, the 13 cases just mentioned, to which may be added four other deliveries elsewhere, indicate that 25 per cent of the women who have had a previous section possess a uterine scar sufficiently strong to withstand the strain of delivery through the natural passages. Naturally, this does not represent the entire truth, as it must be supposed that many of the uteri which were incised at the second or third section would have proven equally as strong had the disproportion not been so marked as to contraindicate any test of labor.

The gross mortality attending the repeated sections was 5.9 per cent. The death of one patient from hæmorrhage was due to the inexperience of the operator; but the other two

TABLE V

Outline of the Clinical History of 13 Cases Delivered Through the Natural Passages Following a Previous Cæsarean Section

Name Number Color Age	Obstetrical history previous to operation	Operation					Pelvis	Labor				Remarks
		Time Place	Indication	Placental attachment	Closure of uterus	Puerperium		Date	Duration	Character	Size of child	
E. W. 2754 Black—34	1899. Podalic version.	1901. Johns Hopkins.	Pelvic dystocia.	Posterior wall.	2 layers. 1. Deep silk. 2. Chr. c. g.	Normal.	G. C. rhachitic. D. C. 10½ cms.	1906	7½ hrs.	Podalic version. 2d stage 2½ hrs.	3335 gm. B. p. 10 cm.	In 1905 delivered in another hospital by forceps.
E. H. 5253 White—25	1908. Abortion—4 months.	1909. Cleveland.	Pelvic dystocia.	.....	.....	Normal (?)	G. C. typical. D. C. 11 cms.	1912	6½ hrs.	Low forceps. 2d stage 1 hr.	3140 gm. B. p. 9¼ cm.	
H. L. 5959 Black—26	.....	1911. Johns Hopkins.	Pelvic dystocia.	Posterior wall.	2 layers chr. c. g.	Febrile.	G. C. rhachitic. D. C. 9½ cms.	1913	18 hrs.	Spontaneous. Premature.	1400 gm. B. p. 7¼ cm.	Uterus removed after Cæsarean in 1914. Scar—Excellent. Wound healed *per primam*. Fever six days.
E. Y. 6927 Black—32	.....	1913. Johns Hopkins.	Eclampsia rigid cervix.	Anterior wall.	3 layers chr. c. g.	Febrile.	.....	1914	15 hrs.	Manual dil. of cervix from 5 cm. Mid forceps.	2080 gm. B. p. 8 cm.	Wound healed *per primam*. Fever two days.
M. G. 7295 White—32	Four labors. All spont. at term.	1913. Chicago.	Toxæmia.	.....	.....	.....	Normal. D. C. not reached.	1915	4 hrs.	Spontaneous.	2780 gm. B. p. 8¾ cm.	
M. S. 7333 Black—19	.....	1914. Johns Hopkins.	Pelvic dystocia. Large child.	Posterior wall.	2 layers chr. c. g.	Febrile.	G. C. typical. D. C. 11 cms.	1915	10 hrs.	Spontaneous.	2915 gm. B. p. 9 cm.	Wound healed *per primam*. Fever nine days.
L. E. 7538 Black—30	Two abortions. Spontaneous. One tubal abortion.	1912. Johns Hopkins.	Prolapsed cord. Cervix 2 cms. dil.	Anterior wall.	3 layers chr. c. g.	Febrile.	Flat rhachitic. D. C. 10½ cms.	1915	20 hrs.	Spontaneous.	3830 gm. B. p. 9½ cm.	Wound infection. Fever six days.
E. R. 8572 Black—29	.....	1913. Philadelphia.	Pelvic dystocia.	.....	.....	.....	G. C. funnel. D. C. 11 cms. T. I. 8 cms.	1917	7¾ hrs.	Spontaneous. Frank breech. Premature.	1980 gm. B. p. —?	
J. S. 9490 White—30	1909. Spont. Stillborn. 1910. Spont. Seven mos. Stillborn. 1911. Spont. Term. d. 6 weeks. 1914. Spont. Seven mos. Stillborn.	1915. Johns Hopkins.	Pelvic dystocia.	.....	2 layers chr. c. g.	Febrile.	Simple flat. D. C. 10¼ cms.	1918	9½ hrs.	Mid forceps. 2d stage 1½ hrs.	2620 gm. B. p. 8¾ cm.	Extra peritoneal Cæsarean. In 1916 spont. at 7 months. Private doctor. Fever six days.
E. M. 9535 White—32	.....	1917. Washington.	Funnel pelvis.	.....	.....	Febrile.	G. C. funnel. D. C. 11¼ cms. T. I. 7½ cms.	1918	33 hrs.	Spontaneous.	3260 gm. B. p. 8½ cm.	Patient said she had "milk-leg." In bed many weeks.
M. T. 10583 Black—21	.....	1916. Johns Hopkins.	Eclampsia rigid cervix.	Posterior wall.	2 layers chr. c. g.	Febrile.	G. C. typical. D. C. 11 cms.	1920	9½ hrs.	Low forceps. 2d stage 1¼ hrs.	3230 gm. B. p. 8¼ cm.	Wound healed *per primam*. Fever for eight days.
E. M. 10917 White—26	.....	1917. Church Home, Baltimore.	Eclampsia.	.....	.....	.....	Normal. D. C. not reached.	1921	27½ hrs.	Induced—Bougie. Convulsions. Spontaneous.	2450 gm. B. p. 8¼ cm.	In 1919 spontaneous at term.
E. C. 10993 Black—19	1917. Spontaneous at term. Difficult labor. Child died from intracranial hæmorrhage.	1919. Johns Hopkins.	Pelvic Dystocia.	Posterior wall.	2 layers chr. c. g.	Febrile.	G. C. rhachitic. D. C. 9¾ cms.	1921	4½ hrs.	Spontaneous.	2750 gm. B. p. 8¼ cm.	Wound healed *per primam*. Fever for nine days.

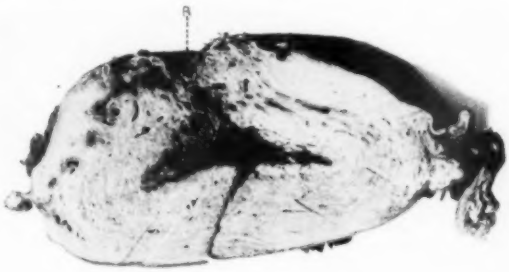
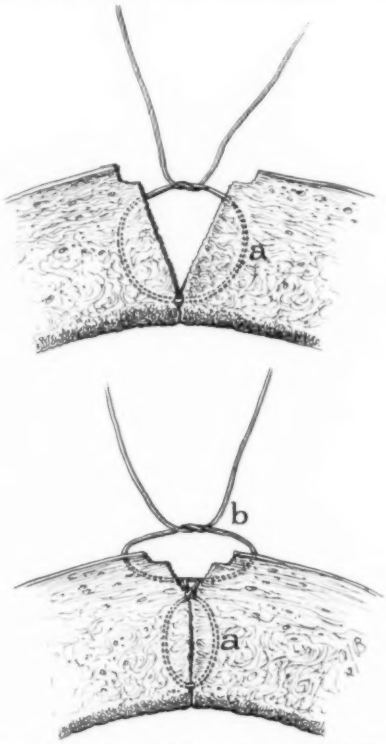
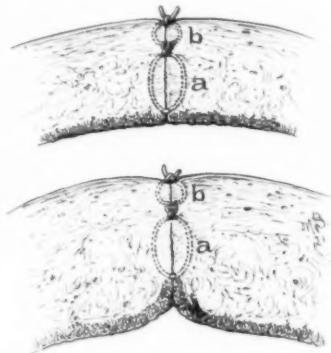


FIG. 1.—Cross-section of uterus removed at autopsy from patient dying from peritonitis (gas bacillus) on third day after operation. Case XI. (A) Site of recent incision. × 3/5.



FIGS. 2 and 3.—Illustrating the two layers of sutures employed in closing the uterine incision. (A) Buried layer. (B) Superficial layer.



FIGS. 4 and 5.—Illustrating a possible cause of imperfect scars. In 4 the sutures have been tightly tied in a relaxed musculature. In 5 contraction has taken place with resulting indentations on both uterine surfaces.

FIG. 6.—Scar from Case I, showing original silkworm gut sutures *in situ* at second section. × 1.

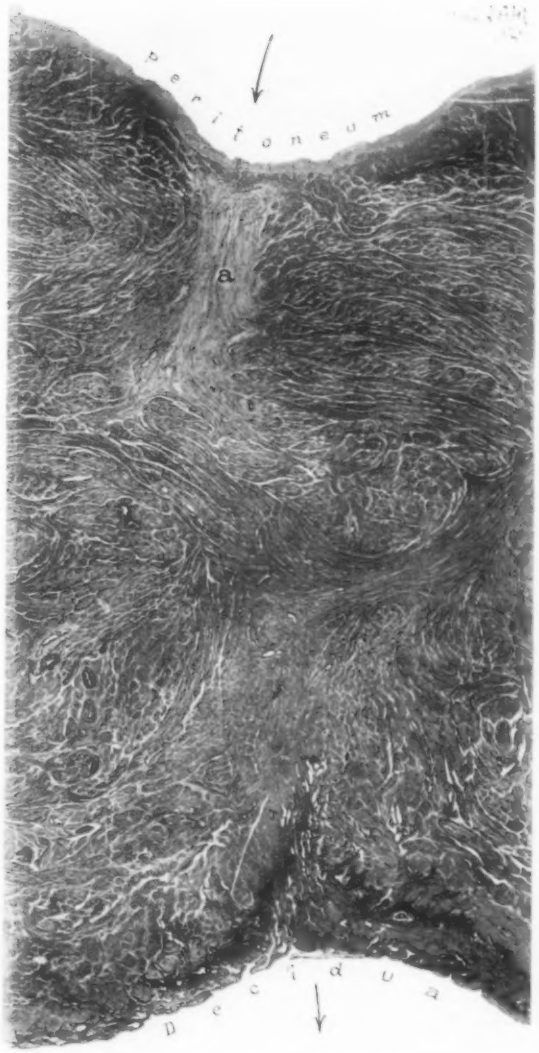


FIG. 7.—Drawing of cross-section of a comparatively well healed Cæsarean scar. It demonstrates the typical depressions on both surfaces of the uterus and the regenerated muscle fibres, with almost no fibrous tissue. × 6.

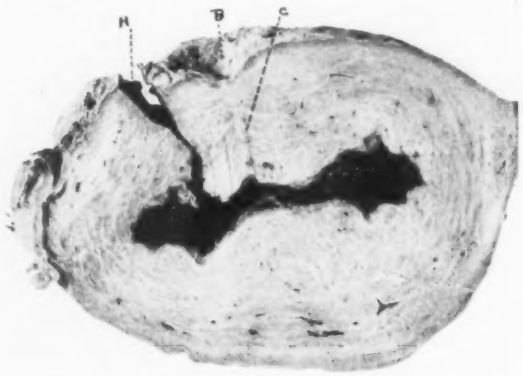


FIG. 8.—Cross-section of uterus from Case I. × ⅔. (A) recent incision. (B) Dense adhesions covering the old scar (C).

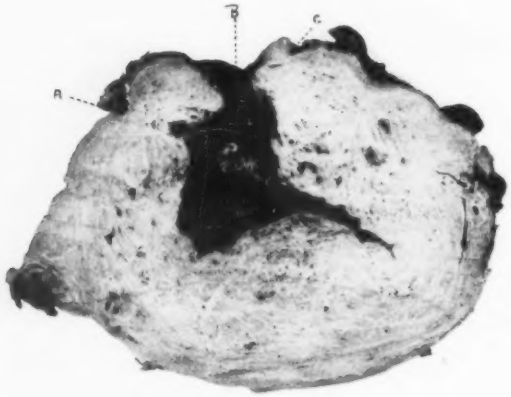


FIG. 9.—Cross-section of uterus from Case II. (A) Old scar. (B) Recent incision. (C) Old scar. × ⅔.

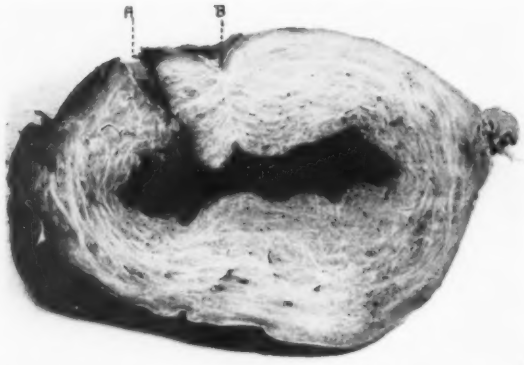


FIG. 10.—Cross-section of uterus from Case III. (A) Recent incision. (B) Old scar. × ⅔.

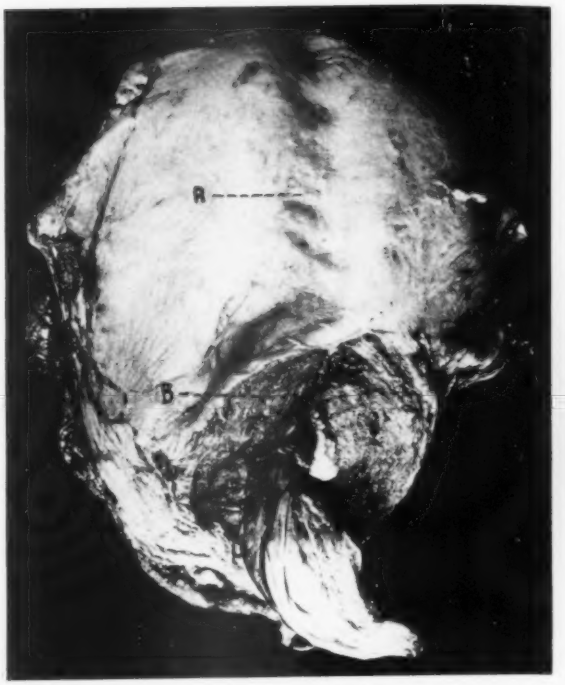


FIG. 11.—Uterus from Case XIII, showing (A) old scar with transverse indentations, and (B) recent incision. × ⅔.

FIG. 12.—Cross-section of uterus from Case XIII. (A) Old scar. × ⅔

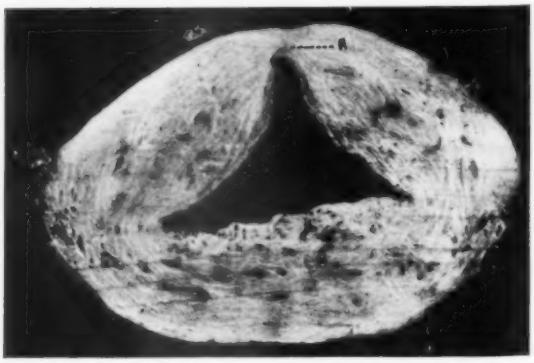


FIG. 13.—Cross-section of uterus from Case XIV. (A) Old scar. × ⅔

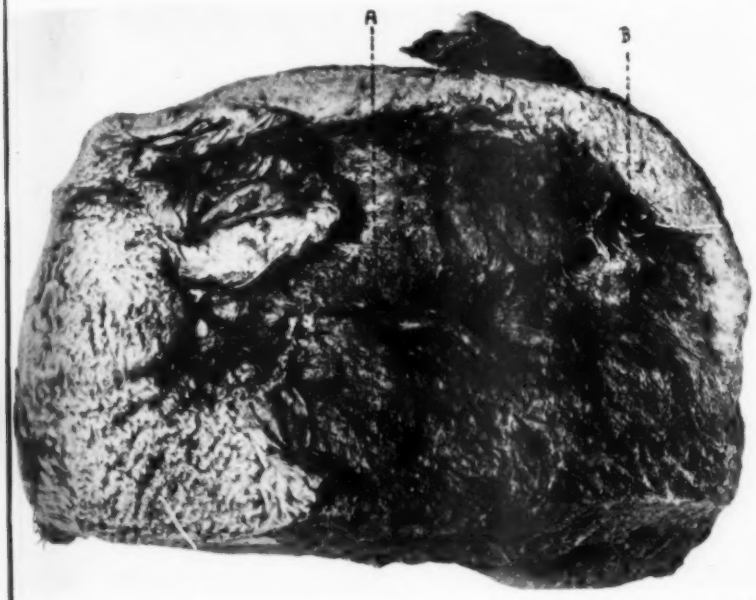


Fig. 14.—Inner surface of uterus from Case XVII. (A) and (B) upper and lower angles of old scar. × ⅔.

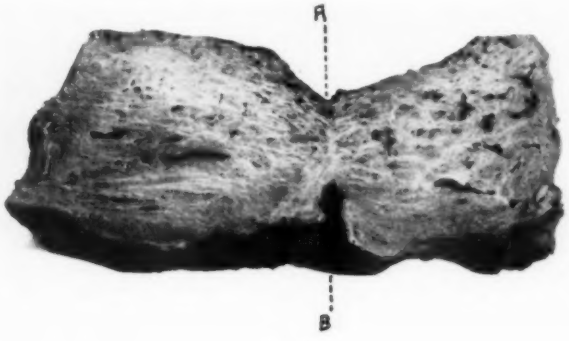


Fig. 15.

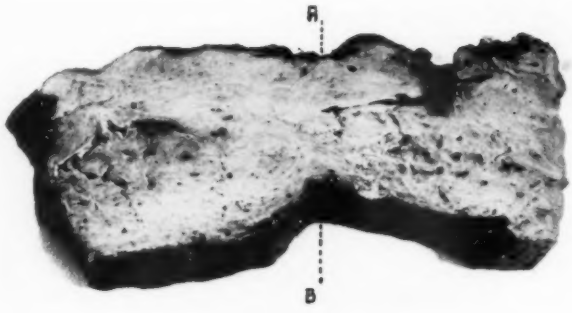


Fig. 16.

Figs. 15 and 16.—Opposite sides of block 1 cm. in thickness from uterus in Case XVII. Shows variation in diameter of scar at various levels. × 1.

Fig. 17.—Cross-section of uterus from Case XIX. (A) Recent incision. (B) Old scar. × ⅔.

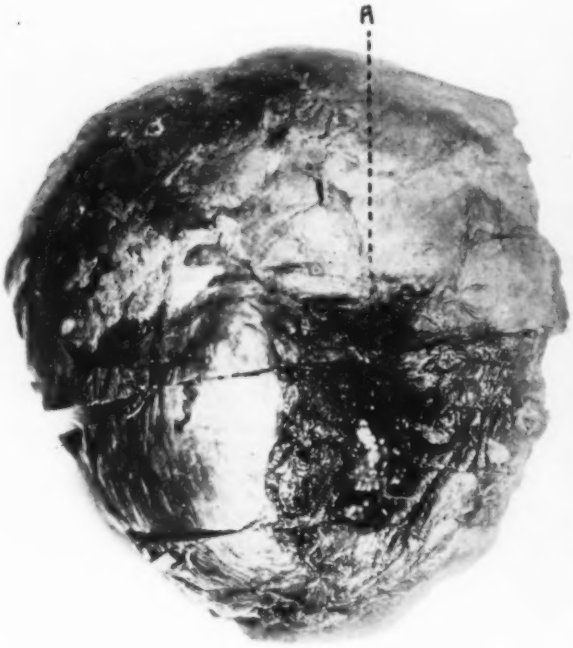


Fig. 18.—Uterus from Case XXI, showing the rupture of old Cæsarean scar. × 1.

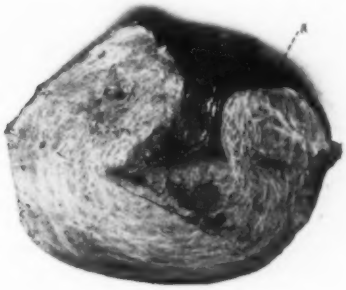


Fig. 19.—Cross-section of uterus from Case XXI. Note the smooth edges of the muscle at the site of rupture. × ⅔.

fatalities were directly attributable to the repeated abdominal operation. Our 48 women went through 63 pregnancies, 13 of which ended by vaginal delivery under our supervision, and 4 elsewhere, with only one instance of rupture of the uterine scar—an incidence of 1 to 63 or 1.5 per cent. It might be argued that this unusually low incidence is due to the fact that we are accustomed to sterilize our patients at the third operation, instead of doing five or six repeated Cæsarean sections, as is the practice of some obstetricians. Doubtless this may play some part in reducing the incidence of ruptured scars, as there can be no question that the greater the number of Cæsarean sections done upon one woman, the greater will be the number of imperfect scars. Consequently, we feel that, after a patient has been subjected to the risk of three major operations, she should be relieved of the added danger of a ruptured scar, which must inevitably become increased after each subsequent operation.

CONCLUSIONS

1. The weak Cæsarean scar may be due to a single factor or to a combination of factors, the most important of which is infection.

2. An afebrile puerperium does not give an absolute assurance of perfect wound healing.

3. The perfection of technique in suturing the uterine incision will undoubtedly lessen the incidence of weak scars.

4. Chromic catgut, in our hands, has proved to be a satisfactory suture material.

5. The uterine wound should not be closed, if possible, until firm contraction of the musculature has occurred.

6. As a rule fœtal elements do not invade the uterine scar.

7. Adhesions following Cæsarean section are common. They are not necessarily the result of coexisting infection, and may give rise to serious complications at subsequent operations.

8. The dictum "once a Cæsarean, always a Cæsarean" cannot be accepted without considerable reservation.

9. A patient who has once been subjected to a Cæsarean section should enter the hospital several weeks prior to the expected date of confinement, so that she may have the benefit of immediate operation should rupture occur.

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ACUTE LOBAR PNEUMONIA AND HÆMATOGENOUS PUERPERAL INFECTION

A CASE REPORT

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The demonstration of a fixed type pneumococcus as the causative agent of a puerperal infection developing during the course of acute lobar pneumonia is unusual, and makes the following case report one of considerable interest both to the obstetrician and internist.

Summary of Case.—*Thirty-five year old primipara; difficult labor with prolonged second stage; chloroform anæsthesia; low forceps delivery; immediate development of signs of acute lobar pneumonia; pneumococcus (type 1) septicæmia; pneumococcus (type 1) endometritis; anti-pneumococcus (type 1) serum therapy followed by rapid disappearance of organisms from the blood stream; prolonged course suggesting "delayed resolution"; recovery from endometritis; serum sickness; suggestive evidence of empyema; terminal hæmolytic streptococcus septicæmia; no autopsy.*

Case Report.—A mulatto housewife, 35 years old, was admitted to the Obstetrical Service February 27, 1921. The family history was negative. The general health of the patient had always been poor. When a child she had had measles, mumps, chicken-pox and possibly pneumonia. At the age of 13 she had recovered after two months from an illness characterized by severe diarrhœa with tenesmus, blood and mucus. She denied having had diphtheria, scarlet fever, rheumatic fever, malaria or typhoid fever. She had suffered from frequent colds and occasional attacks of epistaxis. "Sore throat" had been a frequent winter complaint, and had been usually associated with enlarged tender cervical glands. Six months before admission to the hospital she had suffered for a short time from pollakiuria and dysuria, which had disappeared promptly under medical treatment. Two months before admission to the hospital she had had bilateral suppurative inguinal adenitis, which had been cured by incision and drainage.

Menstruation had begun at the age of 13; it had been regular and of three or four days' duration. The flow had been normal in amount and accompanied by a moderate amount of pain. She had been married in April, 1920, and the last menstrual period had occurred in May, 1920.

Present Illness.—The patient was first seen by one of us in the prenatal clinic on January 11, 1921. At that time she was eight months pregnant with the child lying in the right-occipito-transverse position. The examination of the heart and lungs was negative. The systolic blood pressure was 110; diastolic 70. The incisions in the inguinal regions were healing satisfactorily. The urine was normal and the blood Wassermann reaction was negative. The pelvic measurements were normal. At subsequent visits to the prenatal clinic, on January 26 and February 8, her condition was regarded as satisfactory.

She was admitted to the obstetrical ward in the first stage of labor at 9 p. m. February 27, after having walked several city blocks in a drenching rain. As the temperature was normal and examination of the heart and lungs was negative, she was regarded as being in good condition. Labor progressed satisfactorily until 3 a. m., February 28, when the second stage began. The head soon reached the outlet in the right occipito-posterior position, but as it made very little advance during the next three hours, operative delivery was decided upon. Under chloroform anæsthesia a deeply asphyxiated child was delivered at 6.20 a. m. after a difficult low forceps (Scanzoni) operation—the total duration of labor being 29 hours and 40 minutes. The child was revived by sensory stimulation, and weighed 3380 gm. After the repair of a vaginal laceration, the placenta was expressed from the vagina. Approximately 300 c.c. of blood were lost. The routine microscopic examination of the placenta revealed no abnormalities and a subsequent study of sections stained for bacteria was negative.

The patient left the delivery room in excellent condition. Two hours after delivery, the temperature was 99.4° F., but from then on it rose steadily until it reached 104° F. at 8 p. m. At that time the patient complained of slight pain in the right side of her chest. No chill had occurred, and there was no cough nor sputum, nor were the respirations accelerated. On examination of the lungs a soft pleural friction rub was heard over the right lower lobe, without other changes. Abdominal examination was negative. During the night the temperature fell to 102.5° F., but rose to 104.2° F. the following morning. At that time (March 1) the patient was quite toxic. The respiratory rate was 36 per minute but there was no cough. The breath sounds were slightly suppressed over the right lower lobe and an occasional fine râle could be heard. The abdomen was quite distended and sensitive, but there was no muscle spasm or evidence of fluid. A blood culture was made and 24 hours later was reported positive for the pneumococcus (type 1).

On March 2, the general condition was essentially unchanged. The temperature remained elevated and the patient was quite toxic. Frank signs of consolidation of the lower lobe of the right lung were present. Lochia for intrauterine culture were obtained (by Little's tube), and consisted of a few cubic centimeters of dark serosanguineous fluid. On microscopic examination numerous diplococci were seen, which by culture and by serological examination proved to be pneumococci (type 1). A urine culture, made on March 1, was sterile. The patient was transferred to the medical service March 2, when examination revealed a fairly well nourished tired looking mulatto woman with high fever, tachycardia, moderate cyanosis, and rapid, shallow respiration. There was no cough or sputum. The pulmonary signs were those of consolidation of the right lower lobe. There was

marked distention of the abdomen with considerable tenderness over its lower third, but no muscle spasm or evidence of fluid. Rectal examination revealed a large firm tender uterus. Blood pressure; systolic 125, diastolic 65.

BLOOD EXAMINATION

R. B. C. count	3,393,000
Hæmoglobin (Sahli)	67%
W. B. C. count	6,250
Differential W. B. C. count	(300 cells)
Pm. N.	91.4%
Pm. B.	00 %
Pm. E.	0.7%
S. M.	3.0%
L. M. and T.	2.6%
Myelocytes	2.0%
Myeloblasts	0.3%

With the exception of a trace of albumin and a few white blood cells the urine examinations were negative. The Wassermann reaction (blood) was negative.

Immediately following admission to the ward, anti-pneumococcus (type 1) serum treatment was instituted, as follows:

March 2, 1921, 200 c. c. antipneumococcus type 1 serum intravenously.
March 3, 1921, 200 c. c. antipneumococcus type 1 serum intravenously.
March 5, 1921, 100 c. c. antipneumococcus type 1 serum intravenously.
March 7, 1921, 100 c. c. antipneumococcus type 1 serum intravenously.
March 8, 1921, 100 c. c. antipneumococcus type 1 serum intravenously.

A quantitative blood culture was made (blood-agar plate method) before the first serum treatment, and showed 173 colonies per c. c. of blood, whereas a culture made eight hours later and prior to the second treatment contained but three colonies per c. c. Specimens of blood were likewise taken before the third (March 3, 1921) and subsequent treatments, but were all sterile:

There was no systemic reaction to the intravenous administration of the serum, and the usual chill, leukopœnia and the subsequent abrupt leukocytosis did not appear. However, there was a gradual rise in the number of leukocytes and two days after the first injection they reached 18,000 per c. mm.

With the termination of the septicæmia the patient's general condition improved greatly. The toxæmia became much less evident, and the abdominal distention less distressing. However, the temperature remained elevated and the physical signs in the lungs were essentially unchanged. There was still a moderate degree of pelvic tenderness on abdominal and rectal examination, as well as a fairly profuse, greenish, muco-purulent vaginal discharge. On March 6 (three days after the disappearance of the septicæmia), lochia were obtained for a second intrauterine culture. Smears showed a moderate number of leukocytes and lancet-shaped diplococci, and pneumococci (type 1) were again demonstrated in pure culture.

For two weeks the patient's condition remained practically unchanged, with the exception of a moderate degree of serum sickness, which first manifested itself on March 11. The temperature remained elevated (102.5° F.-104° F.), and the pulse varied between 110-130. The leukocyte count was between 18,000 and 35,000 per c. mm. There was very slight cyanosis and only a moderate degree of abdominal distention. The tenderness over the lower abdomen became much less marked and the vaginal discharge diminished in amount. On March 14 a third intrauterine culture was made and proved to be sterile. It was the opinion of those attending the patient that the prolonged course of the pneumonia was a manifestation of "delayed resolution," and that the uterine complication no longer formed a part of the picture.

On March 16, examination of the lungs showed signs suggestive of encapsulated pleural fluid high in the right axillary region; while the X-ray showed "remains of consolidation at the right base with suggestion of encapsulated fluid in the right axilla." The same equivocal physical and radiographic findings were present the following day. On that day, the 17th, the patient complained bitterly of headache. She was very weak and slept most of the time. Ophthalmoscopic examination showed slight œdema and hyperæmia of the discs, but no other changes. Kernig's sign and neck rigidity were absent, and the reflexes were normal. Nevertheless, a lumbar puncture was performed. Clear cerebrospinal fluid under normal pressure was obtained, and contained ten cells per c. mm. The colloidal gold curve, Wassermann reaction and tests for globulin were negative. The patient's general condition rapidly became worse. The temperature remained high, the rapid pulse became weak and thready, and drenching sweats occurred. Cyanosis became marked and delirium developed. A pelvic examination revealed no abnormalities, and exploratory thoracentesis performed at several different sites in the right axilla and back was negative. A blood culture taken on the evening of this day (March 17) revealed the presence of an overwhelming streptococcus septicæmia—approximately 7600 colonies per c. c. of blood. The patient gradually sank into coma. The pulse and respirations became irregular, and she died on the evening of March 18, the nineteenth day after delivery. Unfortunately permission for an autopsy could not be obtained.

DISCUSSION

The case presents several interesting clinical aspects. The sequence of events seems relatively clear. A primipara, 35 years old, with a past history of numerous infections, and on the whole of rather poor health, entered the hospital for delivery. At the onset of labor she was exposed for a short time to inclement weather. Labor was completed by forceps delivery under chloroform anæsthesia. Immediately following the birth of the child an acute lobar pneumonia developed. As evidence of the lowered resistance of the patient to infection at this time, one might cite the absence of chill and leukocytosis at its onset, and particularly the existence of the septicæmia with large numbers of bacteria in the blood stream (173 colonies per cubic centimeter). Intrauterine culture demonstrated the presence of the same organisms in the post-partum uterus. That this finding was not accidental, or due entirely to the normal oozing of blood infected with pneumococci, is clear; for a greenish mucopurulent uterine discharge developed, which contained numerous white blood cells and organisms. Furthermore, this condition persisted for several days after the disappearance of the bacteræmia, and was accompanied by clinical evidence of uterine infection. Accordingly, it seems clear that we were dealing with a metastatic pneumococcus (type 1) puerperal endometritis, which developed in a woman suffering from acute lobar pneumonia.

When one considers the anatomical and physiological conditions present in the fresh post-partum uterus, one is struck by the fact that it presents a *locus minoris resistentiae*, as Bondy has aptly pointed out, and offers an ideal site for the growth of bacteria seeded into it by a heavily infected blood stream. In our case the puerperal infection obviously did not spread, but remained localized to the interior of the uterus, and had entirely disappeared clinically and bacteriologically by the 14th day. The disappearance of the type 1 pneumococcus bacteræmia following administration of the specific anti-pneumococcus type 1 serum in this case conforms in every respect to the observations of Avery, Chickering, Cole and Do-

chez, and others. That the serum had a beneficial effect upon the local intrauterine infection seems probable; for the process, although caused by a virulent organism and occurring in a patient with obviously lowered resistance, was in itself of rather benign type and of short duration. We feel therefore, that the use of the serum gave the patient a much better opportunity to overcome the infection, as was evidenced by the disappearance of the bacteræmia, the markedly improved general condition, the leukocytosis, the failure of the pneumonic process to spread to other lobes of the lung, as well as by the disappearance of the endometritis.

In concluding the discussion of the case from a clinical point of view, we feel that we may speculate with a fair degree of certainty concerning the terminal process. Although there was suggestive evidence, both from physical findings and radiographic examinations, that an empyema was developing and the prolonged course of the disease confirmed this possibility—repeated exploratory punctures of the pleural cavity failed to substantiate such a surmise. The normal cerebrospinal fluid almost conclusively rules out meningitis as a complication, and there was no evidence of the existence of pericarditis or endocarditis. The pelvic examination made the day before death was normal and the lochia negative. In the absence of a post-mortem examination, we accordingly have to fall back upon the assumption that we were dealing with a patient whose powers of resistance were such that she could not, in the usual length of time, overcome the local pulmonary infection, and as a result of the general debilitation resulting from it became a fit subject for a terminal generalized hæmolytic streptococcus infection, the respiratory tract serving as the portal of entrance. Moreover, it seems likely that the streptococcus pulmonary infection engrafted itself upon the slowly resolving pneumococcus pneumonia, causing an exacerbation of the pulmonary condition and resulted in an overwhelming generalized infection. MacCallum (4) who noted the occurrence of hæmolytic streptococci in three cases of lobar pneumonia studied in army camps, in which pneumococci had been isolated from the blood during the life or from the lungs at autopsy, has suggested the possibility that the latter organisms may have acted as the predisposing agents to infection with the streptococcus.

Pneumococcus Puerperal Infection

The infrequency with which the pneumococcus is encountered as the etiological factor in puerperal infection no doubt explains, to a great extent, the interest with which instances of this condition have been regarded. Bondy, in 1912, published an excellent article upon the subject, which included a report of his own cases and a review of the literature. It is necessary to recall, however, that until comparatively recently the differentiation of the pneumococcus from certain strains of non-hæmolytic streptococci was fraught with difficulty, and that even to-day occasional strains are met with in which the differentiation is not sharply defined. It is, therefore, suggested that statistics compiled before the more recent advances in bacteriological diagnosis were made should be accepted with some reservation, particularly as concerns the reported instances of "primary infection"—or infection by pneumococci gaining access to the uterus by way of the vagina.

It is manifest that two routes are open for the introduction of organisms into the uterus: (1) hæmatogenous (metastatic or secondary), (2) vaginal (primary). We shall consider each in some detail.

Hæmatogenous Pneumococcus Puerperal Infection.—Aufrecht, in 1884, was the first to produce an experimental pneumococcus endometritis by the introduction of living organisms into the blood-stream of rabbits shortly after labor. At autopsy a localized uterine pneumococcus infection was found with but insignificant changes elsewhere. Thus he proved experimentally that the puerperal uterus in that animal is a *locus minoris resistentiæ*, and that the pneumococcus is capable of producing pathological lesions in it. Orthmann (referred to by Bondy) confirmed this work. Weichselbaum, in 1888, reported the first instances of hæmatogenous pneumococcus infection of the puerperal uterus in women. Both occurred in patients suffering from acute pulmonary infections (exudative pleurisy and pneumonia). At autopsy the pneumococcus was found in the endometrium, as well as in the primary focus in the respiratory system. Bondy refers to the instance reported by Bumm in 1899, in which a pneumococcus peritonitis was associated with pneumonia and empyema. At autopsy pneumococci were demonstrated in the uterine blood vessels and secretions. Burchardt, in 1901, reported an instance of premature labor during the course of acute lobar pneumonia, in which pneumococci were found in the placental site and lymphatics of the uterus. Furthermore, Foa and Bordoni-Uffreduzzi cite two instances of abortion in pneumonic women in which pneumococci were found in the uterine veins. Stanoskiadis, in 1913, reported 12 cases of lobar pneumonia in which pneumococci were found in the vaginal secretions: He considered that they represented instances of hæmatogenous infection which was favored by the changes incident to abortion or delivery. Haller, Oertel and others have likewise discussed the subject.

In the light of the above reports, as well as of our own case, is seems profitable to recall that in 728 cases of acute lobar pneumonia reported by Cole, in which blood cultures were made, 27.8 per cent were positive for the pneumococcus. In other words, he demonstrated that a pneumococcus bacteræmia is probable in approximately every fourth case of pregnancy which is complicated by lobar pneumonia. Under these conditions the possibility of a pneumococcus infection of the uterus at the time of, or shortly after, its evacuation does not seem remote, and should be borne in mind by obstetrician and internist alike.

Vaginal (Primary) Pneumococcus Puerperal Infection.—Although our case obviously does not fall into this group, a brief survey of the subject may prove of interest. As has been intimated, our knowledge of the pneumococcus has been considerably extended during recent years, and the organism can now be more easily and accurately differentiated from other cocci. Allowances must, therefore, be made in interpret-

ing the results of investigators who worked prior to the acquisition of this knowledge.

It would seem that the pneumococcus is very rarely an inhabitant of the normal vagina. Bondy, in 1912, failed to find it in a search of the vaginal flora of 30 non-pregnant women, but found it once in the same number of normal pregnant women, as well as once in the lochia from 30 postpartum patients. Fabret and Bourret called attention to this work in 1913, and regarded it as affording conclusive evidence that the pneumococcus is not an inhabitant of the normal vagina. On the other hand, Schottmüller in 1910 found pneumococci in the lochia of three per cent of his cases of septic abortion; while Foulerton and Bonney in their examination of 54 puerperal women found pneumococci in four instances.

That the pneumococcus may occasionally be present in the vagina of the pregnant and puerperal women cannot be doubted, and in the light of the cases collected by Bondy and by Fabret and Bourett it seems certain that it may, under certain conditions, find its way into the postpartum uterus and there give rise to puerperal infection. The reader is referred to articles by the last named authors for an extended discussion of this question.

TREATMENT

Beside the general supportive measures usually employed in puerperal infections, Moore has suggested that uterine irrigations with ethylhydrocuprein (optochin), 1:10,000, may possibly be used to advantage, on account of the powerful antipneumococcus properties of the drug. If the infection is due to a type 1 organism, intravenous serum therapy may be indicated. In our case the uterine infection was of moderate degree so that local treatment was not attempted, but all of our efforts were directed to the relief of the pulmonary condition. However, we feel that the serum treatment was perhaps incidentally responsible for the mildness of the uterine infection and its early disappearance.

SUMMARY

We have reported a case of acute lobar pneumonia (pneumococcus type 1) with septicæmia as a complication of the puerperium, and have shown that a hæmatogenous (pneumococcus, type 1) endometritis developed and disappeared under, observation. Death occurred on the 19th day from generalized hæmolytic streptococcus infection.

A brief review of the literature upon pneumococcus puerperal infections is given, and instances of both secondary (hæmatogenous) and primary (vaginal route) types are cited. It is suggested that the possibility of a pneumococcus puerperal infection should be borne in mind when dealing with patients in whom abortion or term delivery has occurred during the course of acute lobar pneumonia.

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DIPHTHERIA BACILLUS CARRIERS

RESULTS OF RE-EXAMINATION OF APPARENTLY NEGATIVE CULTURES

By B. C. Marshall and C. G. Guthrie

(From the Division of Clinical Pathology of the Medical Clinic, The Johns Hopkins University and Hospital)

As ordinarily practiced, the examination of throat cultures for the presence of diphtheria bacilli is made after incubation of the tubes for from 12 to 24 hours, usually over night. Not infrequently a positive result may be obtained much sooner than this and in special cases examinations are made at intervals beginning at six hours, but it is quite generally the custom to discard as negative all cultures in which diphtheria bacilli have not been found after 24 hours in the incubator. This custom has probably arisen from several causes, as for instance:

1. The desire to secure positive information as early as possible.

2. The belief that the growth of the diphtheria bacillus on a suitable medium is relatively rapid during the first 24 hours, but that after that time it is apt to be overgrown by the other organisms encountered in cultures from the throat.

3. The belief that the morphology of the diphtheria bacillus is characteristic only during the earlier period of its growth on even the best of media; that after 24 hours its staining properties are lost to a greater or less degree and involution forms may appear, thereby rendering its recognition difficult or impossible in mixed cultures from the throat.

4. The belief that if diphtheria bacilli have not been found in the examinations of a throat culture during the first 24 hours they will not appear subsequently in that culture and therefore that search made at a later time would merely entail useless routine work.

We have no criticism to offer concerning examination of throat cultures "early and often," but we believe that the practice of regarding as negative all cultures which have not shown diphtheria bacilli up to 24 hours may yield results which are misleading, particularly in the case of bacillus carriers.

In the course of some experimental work with the so-called "elective medium" of Drigalski and Bierast.* we found that a number of the tubes, considered negative at 24 hours, were positive when re-examined a day later. It naturally occurred to us that the apparent delay in development of the diphtheria organisms might be due to the inhibitory effect of the bile in the special type of medium employed, but it soon became evident that a similar retardation might occur with other sorts of media as well. After this point was established we made it a rule to examine all cultures both at 24 and at 48 hours.

* v. Drigalski and Bierast: Nachweis der Diphtheriebazillen und seine praktische Bedeutung. Deutsche med. Wchnschr., 1913, XXXIX, 1237. This medium consists essentially of Loeffler's blood serum to which a certain amount of bile has been added prior to coagulation. The object of the addition of bile is to inhibit the growth of the other organisms from the throat without interfering with the growth of the diphtheria bacillus.

At this time we had under observation a series of diphtheria bacillus carriers—some of them healthy, others convalescent carriers, some who harbored virulent and others non-virulent organisms—and from these persons throat cultures were taken daily over a period of several weeks. The cultures were made on several different kinds of blood serum media and were examined with great care. All of the cultures found negative at 24 hours and almost one-half of the positive ones were re-examined at 48 hours. The results are presented in Tables I, II and III.

TABLE I

Results of Cultures Examined after Incubation for 24 and 48 Hours

Cultures	Examined after incubation for 24 hours		Re-examination at 48 hours of cultures negative at 24 hours		Re-examination at 48 hours of cultures positive at 24 hours	
	Number	Per cent	Number	Per cent	Number	Per cent
Total.....	759	.....	549	.....	93	.....
Positive....	210	27.66	52	9.47	92	98.92
Negative...	549	72.33	497	90.52	1	1.07

TABLE II

Analysis of Positive Results

Cultures	Number	Per cent
Total positives.....	262	.....
Positive at 24 hours.....	210	80.15
Positive only at 48 hours.....	52	19.84

TABLE III

Virulence of Diphtheria Bacilli in Cultures Positive Only at 48 Hours

Medium	Virulent strains	Non-virulent strains	Total
Loeffler (pig serum).....	24	20	44
Loeffler (beef serum).....	1	1	2
Drigalski and Bierast (pig serum + bile).	3	0	3
Drigalski and Bierast (beef serum + bile).	3	0	3
Total	31	21	52

From Table I it is seen that of the 759 cultures from these carriers, 210, or 27.66 per cent, were positive at the first examination made after approximately 24 hours' incubation. Five

hundred and forty-nine cultures were negative at the first examination and of these 52, or 9.47 per cent, were positive when examined after an additional incubation of 24 hours. Re-examination of 93 originally positive cultures showed that 92 were still positive after 48 hours in the incubator.

An analysis of the positive results (Table II) shows that of the 262 cultures in which diphtheria bacilli were found, 210, or 80.15 per cent, were positive at the first examination, and that 52, or 19.84 per cent, were found positive only at the second examination which was made 24 hours later.

From Table III it is seen that among the 52 cultures found negative at the first examination but positive at the second, 31 contained virulent and 21 contained non-virulent strains of diphtheria bacilli. These 52 cultures were made on four different kinds of serum media, on all of which the diphtheria bacillus grows admirably when pure and, as a rule, also when it is present in mixed culture from the throat.

These results speak for themselves and require little comment. From them it is evident that practically one-fifth of the total number of positive cultures were regarded as negative when examined at 24 hours, but were shown to contain diphtheria bacilli when examined a day later. In all instances the original slides were saved for re-examination in case the culture should prove positive at 48 hours. Careful search showed the original report to have been justified in almost every instance, but whenever this re-examination revealed any diphtheria bacilli in the 24 hour slides, the earlier diagnosis was changed and such cases are omitted from this series. It is perhaps unnecessary to add that tubes which showed little or no growth at 24 hours are not included, even though subsequent examination may have revealed the presence of diphtheria bacilli. The practice of examining throat cultures both at 24 and at 48 hours has been continued since these figures were collected and the additional experience of several years has shown the advantage of this procedure. Since introducing it in this laboratory we have isolated typical Klebs-Loeffler organisms from 75 or more of these "delayed positives," thereby confirming the diagnosis originally based on morphology alone. The difference in morphology at 48 hours is practically negligible, being, when it occurs at all, in the nature of an increase in the number and size of the Babes-Ernst granules, thereby facilitating recognition of the organisms when the Neisser or similar contrast stains are used. In general, the development of involution forms seems to be less marked in mixed cultures from the throat than in pure cultures.

In our experience the "delayed positive" culture has been found only among carriers, healthy or convalescent, and has been quite independent of the virulence of the strain of organisms present in the throat. In cases of clinical diphtheria we have practically always found the organisms abundant and their recognition easy in throat cultures incubated for 24 hours, so that no difficulty exists from the source we have mentioned in the bacteriological diagnosis of actual cases of the disease.

The explanation of the "delayed positive" culture is far from clear. Whether the diphtheria bacilli present in cultures from the throat of carriers may have a more prolonged period of lag than those from patients in the acute stage of the disease we are not prepared to say. In many instances this is obviously not the case, as the cultures may show at the first examination an abundant growth consisting almost exclusively of diphtheria bacilli. The organisms present in the "delayed positive" cultures, moreover, show a normal rate of growth when isolated in a pure state. We can only suggest that this peculiar retardation may possibly be due to the inoculation of the culture with a very small number of viable diphtheria bacilli and a very large number of other organisms which temporarily overgrow or possibly inhibit the former. Almost invariably, when Klebs-Loeffler bacilli were found to be sparse at 24 hours, they were abundant at 48 hours; if originally numerous, they were much more plentiful on the following day. In only one instance was a culture which was positive at 24 hours found negative at 48 hours. When once the diphtheria bacillus starts to grow, it apparently is able to hold its own against most of the other bacteria encountered in throat cultures with the exception of the hay bacillus and certain similar organisms. Many cultures have been examined after periods of growth longer than two days, but no evident advantage was found in this procedure.

Similar observations have been made by other workers. Knebel * collected some interesting statistics at the Hygienic Institute in Frankfurt; the results which form the basis of his report have been condensed and are shown in Table IV.

TABLE IV

RESULTS OF EXAMINATION OF THROAT CULTURES AFTER INCUBATION FOR ONE DAY AND TWO DAYS

(From Knebel)

Source of cultures	Result after incubation for one day		Result after incubation for an additional day		
	Negative	Doubtful	Negative	Doubtful	Positive
Fresh diphtheria suspects.	...	62	43	7	12
Convalescents.....	...	56	23	17	16
Fresh diphtheria suspects.	159	..	151	7	1
Convalescents.....	576	..	470	51	55

From Knebel's figures shown in Table IV, it is seen that of the throat cultures from 118 cases—62 fresh suspects and 56 convalescents—all of which were recorded as doubtful at the first examination, 28 were definitely positive, 66 were definitely negative and only 24 were still considered doubtful when examined a day later.

Table IV also shows that of 159 throat cultures from diphtheria suspects regarded as negative at the first examination, only one was found positive after incubation for another day and in this isolated instance both the history and the physical examination of the patient suggested strongly that they were

* Knebel, Max: Beiträge zur bakteriologischen Diagnose und Statistik der Diphtherie. Inaugural Dissertation, Giessen, 1912.

dealing with a convalescent rather than a fresh case of diphtheria. Further information is available concerning four of the seven cases which were reported as doubtful at the second examination; the organisms from two of these were shown not to be diphtheria bacilli; attempts to isolate the organisms seen in the culture from another were unsuccessful; the pure culture obtained from the fourth proved to be avirulent on animal inoculation.

Conditions were quite different, however, with regard to the 576 negative cultures from convalescents; 55 or 9.54 per cent, proved to be positive when examined next day and these findings were confirmed by further study including virulence tests on the organisms obtained in pure culture. The originally negative cultures from 51 cases which were moved to the doubtful column as the result of the second examination, Knebel dismisses with the comment that a doubtful result is of much less importance in a convalescent than in a diphtheria suspect and that, when dealing with convalescents, one cannot go wrong provided prophylactic restrictions are not relaxed on the basis of a doubtful answer.

Neisser,* who was director of the Frankfurt Institute speaks favorably of Knebel's report and recommends that (1) all cultures showing a poor growth after incubation for one day and (2) all throat cultures from convalescents should be re-examined on the following day.

Seidel † also lays stress on the desirability of examining all throat cultures from convalescents both at 20 and at 44 hours. He cites an instance in which failure to re-examine a culture which was negative at 20 hours resulted in the discharge of a convalescent child who promptly infected her three little sisters.

* Neisser, M.: Bakteriologie der Diphtherie. Centralbl. f. Bakteriol., 1913, Section 1, LVII, Supplement, p. 1. Neisser, M., and Gins, H. A.: Ueber Diphtherie, *in* Kolle and Wassermann's Handbuch der Pathogenen Mikroorganismen, Ed. 2, Jena, Gustav Fischer, 1913, V, 931.

† Seidel, Otto: Zur Behandlung der Diphtherie, München. med. Wchnschr., 1915, LXII, 1209.

A comparison of our results with those reported by Knebel is presented in Table V.

TABLE V

Comparison of Our Results with Those Reported by Knebel

Source of cultures	Cultures negative at 24-hour examination	Cultures positive when examined at 48 hours	
		Number	Per cent
Diphtheria convalescents (Knebel)...	576	55	9.54
Bacillus carriers, convalescent or healthy (Marshall and Guthrie).	549	52	9.47
Total.....	1125	107	9.51

From Table V it is seen that our figures agree very closely with those reported by Knebel, although his observations were made entirely upon patients convalescent from diphtheria, whereas ours were made upon bacillus carriers, some of them convalescent but others healthy carriers.

From these results it seems evident that, when dealing with throat cultures from diphtheria carriers, the customary laboratory practice of making single or repeated examinations within the first 24 hours may not yield all of the information available and may lead to erroneous conclusions. The error from this source alone, as judged from the results in 1125 cases, is about 9.5 per cent. If one is interested in determining the duration of the carrier state, in ascertaining the actual condition of affairs, rather than in merely securing some arbitrary number of successive negative cultures required by health regulations prior to discharge of a patient, further investigation is essential.

It is to be recommended, therefore, that in the study of diphtheria bacillus carriers, either healthy or convalescent, all cultures which are negative up to 24 hours be re-examined after another day in the incubator.

THE HYDROGEN-ION CONCENTRATION OF TISSUE GROWTH *IN VITRO*

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Introduction

Before undertaking a study of the effect of bacteria upon growth of tissue culture, it seemed necessary to determine in what way media of different H-ion concentrations influence the activity of tissue cultures, and whether there is a parallelism between what we know of the determining factor of H-ion concentration on the life process of micro-organisms and on cultures of embryonic tissue. Numerous observers have shown that there is both an optimum H-ion concentration for bacterial growth and a limiting or final concentration at which growth activity is at rest, both conditions being influenced by the constituents of the medium. It was our purpose, therefore, to determine the optimum and the limiting or final H-ion concentration for tissue cultures, and to show any possible similarity of metabolism between pure type embryonic connective-tissue cells and cellular organisms (bacteria) as grown *in vitro*. At the present the comparison must of necessity be crude, both because of the different conditions under which the two types of living cells exist and because of our meager knowledge concerning the elements necessary for life and propagation of cells.

TECHNIQUE

Explants of chick embryos in Locke-Lewis solution furnished a satisfactory means of following the hydrogen-ion concentration during the growth of tissues, because of the ease with which a medium of a given H-ion concentration can be prepared and its fluidity at all ages of growth, in contradistinction to plasma. After some experimentation, a colorimetric method was devised (Felton, 1921) by which it was possible to test out the small hanging drop of the tissue culture. This method is not only very simple but also apparently quite exact. A drop of indicator of approximately the same size as the hanging drop was placed directly upon the growth on the cover-slip, shaken or stirred about and, with an abrupt blow, shaken off into a white glass plate. An exact reading of the drop was then obtained by combining a drop of indicator with a drop of a known buffer solution until the same color as that of the hanging drop was obtained.

Tissue cultures were prepared in the usual manner (Lewis and Lewis, 1915). Locke-Lewis solution (85 c. c. of NaCl 0.9 per cent plus KCl 0.042 per cent plus $CaCl_2$ 0.025 per cent plus $NaHCO_3$ 0.02 per cent plus 15 c. c. chicken bouillon plus 0.25 per cent dextrose) has a H-ion concentration between 6.6 and 7, usually 6.8. When a medium of a given H-ion concentration was to be prepared, the sodium bicarbonate and dextrose were omitted and sodium hydroxide or hydrochloric acid was added until the solution, when tested after boiling for 15 minutes, gave the color corresponding to that of the buffer solution of the required H-ion concentration. To this was then added sufficient dextrose to make 0.25 per cent. Solutions of H-ion concentrations varying from 4.4 to 9.2, with an increment of 0.2, were used. Explants were made from connective tissue from chick embryos ranging from 5 to 14 days' incubation, but unless otherwise stated the results refer to tissue from embryos of 7 to 9 days' incubation.

The buffer solutions used in these experiments were furnished by Doctor W. Mansfield Clark. The indicators were thymol blue, methyl red, brom thymol blue, brom cresol purple, phenol red, cresol red, and phenolphthalein.

VARIABILITY OF THE H-ION CONCENTRATION OF LOCKE-LEWIS SOLUTION ON DIFFERENT KINDS OF COVER-SLIPS

A few series of cultures sufficed to show that care must be taken in selecting the cover-slips for these experiments. With cover-slips made from certain kinds of glass the control hanging drops, after incubation, varied greatly and many of them became so alkaline that the results of any experiments with different media would have been obscured. All cover-slips were placed in dilute sulphuric acid for one or more days before preparing them for use. Covers of three unknown makes, which had been in the laboratory a number of years, were the most satisfactory. When a drop of a solution of a known H-ion concentration was incubated upon these it remained almost unchanged for a number of days, so that after a period of three weeks in the incubator the H-ion concentration was approximately the same as that of the original solution (6.8 to 7.0). A number of other kinds of cover-slips were tested but proved to be unsatisfactory for our purpose, as the hanging drop sometimes changed within a few days from pH 6.8 to pH 8 or 8.6. It is clear, therefore, that the selection of cover-slips suitable for the purpose is of great importance before undertaking any experiments.

An attempt was made to render the unreliable cover-slips more satisfactory by coating them with celloidin or with paraffin. Those covered with a thin layer of celloidin were favorable for growth; the cells grew out as extensively and lived as long on such covers as on the usual ones, but the hydrogen-ion concentration of the control drops still varied greatly, due no doubt to the dialysis of the H-ion from the glass. It is possible that an impermeable membrane would produce almost ideal conditions. The alkalinity of these drops did not increase to such a marked extent as on the uncoated cover-slips, but the variations in the results with the individual cover-slips was so great as to render them undesirable for these experiments. On the cover-slips coated with paraffin the drops remained much more constant, but rounded up to such extent that such covers were useless for the purpose of tissue cultures. The limited number of reliable cover-slips obtainable at this time accounts for the small number of experiments given in the charts.

RANGE OF HYDROGEN-ION CONCENTRATION OF MEDIA IN WHICH CHICK TISSUE EXHIBITED GROWTH

Pieces of chick embryos were explanted into media having a H-ion concentration varying from 4 to 9.2, with an increment of 0.2. In solutions having H-ion concentrations of 4.0, 4.4, 4.8, 5.0 and 5.2 no growth was obtained, except in one series in which a few migrating cells wandered out from explants of a 68-hour embryo in a solution of pH 5.0. Many explants, from embryos of all ages, were made in solutions of pH 5.5, but none of these grew except in the case of a chick blastoderm of 24 hours' incubation. In general, the younger the embryonic tissue the greater the percentage of growth in media of low pH value.

Approximately one hundred cultures were explanted into solution with H-ion concentrations of 6.0, 7.0, 8.0 and 9.0. The percentage of growth which occurred in these cultures was respectively 71, 93, 89 and 81. In the normal Locke-Lewis solution, which has a H-ion concentration usually about 6.8, over two hundred cultures were explanted. Of these, 90 per cent grew. The greatest number of cultures grew in media of pH 7 and in the normal solution, and these cultures also exhibited the most extensive growth. It was frequently impossible to differentiate the series of cultures explanted into media having a H-ion concentration of 7.0, 7.2, and 7.4. What growth took place in solutions of pH 6.0 was extensive and healthy, but tissue from embryos of over 11 days' incubation seldom grew in this medium. The growth in solutions of pH 9.0 was frequently small, whereas that in solutions of pH 8.0 was more extensive and lived longer.

Hydrogen-ion Concentration of Cultures Grown in Media of Varying Hydrogen-ion Concentrations (pH 6, 7, 8, and 9)

Table 1 shows the results obtained when cultures explanted into solutions of different hydrogen-ion concentrations (pH 6.0, 7.0, 8.0 and 9.0) were tested by means of the drop colorimetric method described above. While the individual cultures varied greatly, there were no marked differences by which cultures belonging to one series could be distinguished from those of another. Cultures explanted into acid media (pH 6.0) were on the whole somewhat more acid than those in normal Locke-Lewis solution, while those explanted into alkaline media (pH 9.0) were a little more alkaline than those in neutral solutions.

The lack of any marked differences between the series of cultures was probably due largely to the fact that the explanted piece acted as a buffer, so that shortly after explantation the medium became changed to one more nearly neutral. This was especially so in the alkaline solutions. Cultures explanted into media, which, after explantation, had a H-ion concentration of 8.2 and 9.0, became within 3 to 4 hours pH 6.8 to 7.2 and pH 7.6 to 8.0, respectively. Not enough cultures were examined to justify any definite conclusions, but from the table it is evident that, regardless of the initial hydrogen-ion concentration of the medium, cultures which contained healthy and extensive growth tended to be neutral, those which failed to grow had usually become slightly acid, and those which had exhibited extensive growth and then degenerated were slightly alkaline. As will be shown later, however, this last point depends upon the amount of dextrose present in the medium.

It is difficult to understand what factors caused our results to differ from those obtained by Rous (1913), who studied cultures of chick embryo tissue explanted into plasma that had been colored blue with litmus. The differences in regard to healthy cultures may be explained on the ground that diffusion takes place much less readily in plasma than in Locke-Lewis solution; therefore, whatever acid was produced by the explant may have been held in the immediate vicinity of the explant and thus have become condensed to a sufficient strength to turn the blue litmus pink. This, however, does not account for the fact that in Rous's experiments cultures that failed to grow remained alkaline, while in ours such cultures were usually more acid than those exhibiting good growth. The varied results may be explained upon the basis of different media.

Hydrogen-ion Concentration of Cultures Grown in Locke-Lewis Solution

The hydrogen-ion concentration of the solution used depended upon that of each preparation of bouillon. It was usually about 6.8, but in a few instances was 6.6, and in others 7.0. The amount of dextrose added to the solution varied, as it was measured, not weighed; supposedly about 0.25 per cent to 0.5 per cent dextrose was used. Two hundred and thirty-six cultures were tested in this solution (Chart 1). Of these, 19 failed to grow, 107 exhibited extensive growth, and 110 were tested after the growth had degenerated.

The age at which the culture was tested had little bearing upon the hydrogen-ion concentration. The condition of the culture, on the other hand, appeared to have a marked influence, as it was found that cultures that had failed to grow were usually slightly acid. The greater number of those tested when the growth was extensive and healthy were neutral, with a range from pH 6.6 to 7.4; whereas, after degeneration had taken place, most of the cultures were slightly alkaline, ranging from pH 6.0 to 7.8.

Influence of Dextrose in the Medium upon the Hydrogen-ion Concentration of the Cultures

Tissues grew extensively in media containing from 0.25 per cent to 2 per cent dextrose. When dextrose was omitted from the solution, the cultures often exhibited an extensive cell proliferation within 24 to 48 hours, but soon became full of vacuoles, and degeneration took place within a few days (Lewis, 1921). When a large quantity (4 to 5 per cent) dextrose was added, the amount of growth was quite variable; sometimes large, again small, and in some instances consisting of only a few migrating cells. The cells of this growth, however, seldom contained any vacuoles, even after many days. The growths in media containing a large amount of dextrose usually lived longer (1 to 2 weeks) than those in media without dextrose (3 to 5 days), but seldom as long as those in cultures containing a smaller amount of dextrose (2 to 4 weeks).

It was difficult to determine the exact amount of dextrose most favorable for the cultures. It varied between 0.5 per cent and 1 per cent, depending upon the series; in some experiments, culture in a medium containing 0.5 per cent dextrose exhibited larger growth and lived longer than those in a solution to which 1 per cent dextrose had been added, while in other series the results were reversed. From an examination of the numerous cultures (over 500) explanted into media containing different percentages of dextrose, it was found that 0.25 per cent was seldom sufficient sugar to maintain a healthy growth for many days. The cells began to develop vacuoles within 4 to 5 days and died shortly afterwards.

Of the cultures explanted into media without dextrose, 71 were tested at death. Of these 19 had a hydrogen-ion concentration of 7, 34 were pH 7.2, 15 were pH 7.4 and 3 were pH 7.6. The longest period of life was 9 days; the greater number of the cultures died between the third and fifth day. Most of the solutions used as media had a hydrogen-ion concentration of 6.4 and 6.6; a few were pH 6.8 or pH 7.0. When dextrose was not added to the medium the cultures did not become acid during growth and degeneration. Those failing to grow, however, were slightly acid.

As shown in Table I, Chart I, and Table II, cultures containing 0.25 per cent to 0.5 per cent dextrose behaved in somewhat the same manner. On the other hand, cultures in media containing 1 per cent or more dextrose usually had become acid at death. The range of hydrogen-ion concentra-

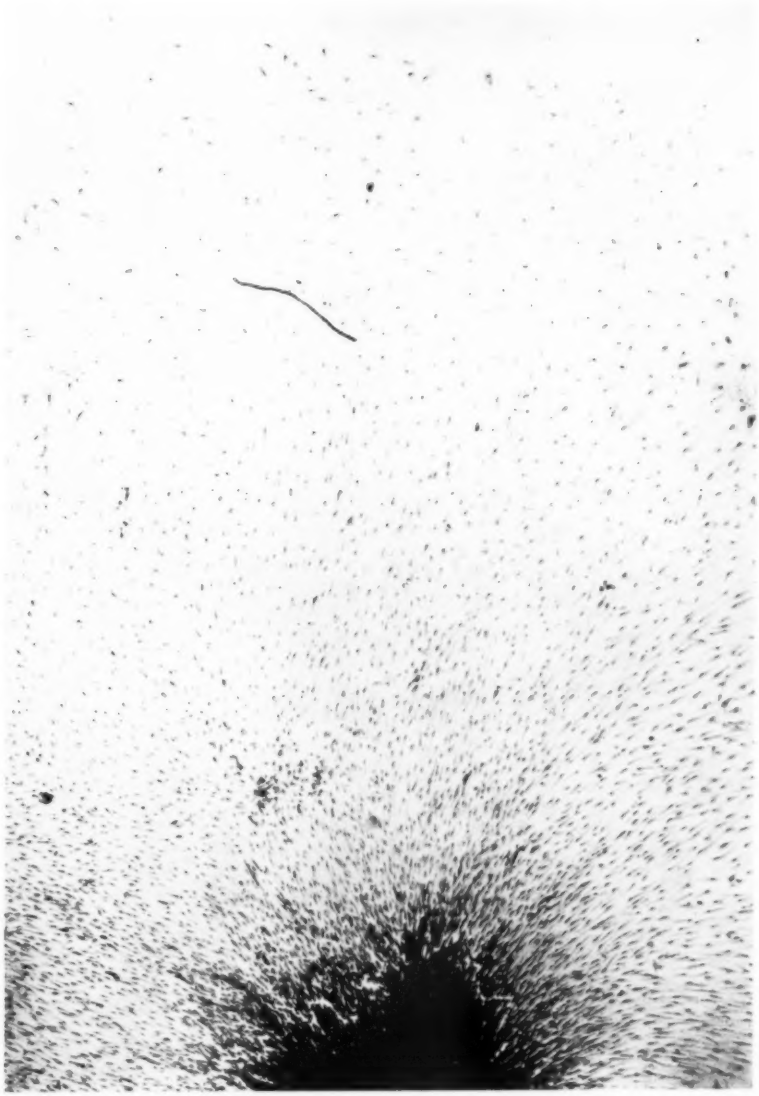

FIG. 1.—A 7-day culture of connective tissue from an 8-day chick embryo. The dark area is the explanted piece and the distance from this to the cells at the top of the page may be used as an axis to indicate the extent of the outgrowth of cells which is meant by extensive growth. × 43.

tion varied greatly in the different cultures. Usually, cultures that contained the most dextrose were the most acid. Those in 5 per cent dextrose (the largest amount of sugar used in these experiments) were frequently pH 5.8 to pH 6.0. The length of life of the growth in cultures containing more than

TABLE I

HYDROGEN-ION CONCENTRATION OF

The medium	The cultures after 3-4 hours	Failed to grow	Extensive growth	Large growth, later died
pH 6	5 were pH 6.4	3 were pH 5.8 13 " " 6. 12 " " 6.2 3 " " 6.4 1 was " 6.6 1 " " 6.8	5 were pH 6.4 17 " " 6.6 8 " " 6.8 1 was " 7.	2 were pH 6. 2 " " 6.2 2 " " 6.4 8 " " 6.6 7 " " 6.8 6 " " 7. 8 " " 7.2 4 " " 7.4
pH 7	10 were pH 6.8	2 were pH 6.2 4 " " 6.4 3 " " 6.6 2 " " 6.8	1 was pH 6.6 5 were " 6.8 3 " " 7.	1 was pH 6. 1 " " 6.2 1 " " 6.4 7 were " 6.6 11 " " 6.8 7 " " 7. 11 " " 7.2 7 " " 7.4 3 " " 7.6 1 was " 7.8
pH 8	4 were pH 6.8 6 " " 7. 4 " " 7.2	6 were pH 6. 2 " " 6.6 2 " " 6.8 1 was " 7.	1 was pH 6.4 9 were " 6.6 13 " " 6.8 11 " " 7. 2 " " 7.2	2 were pH 6.4 6 " " 6.6 7 " " 6.8 6 " " 7. 14 " " 7.2 6 " " 7.4 12 " " 7.6 5 " " 7.8
pH 9	1 was pH 7.2 2 were " 7.4 3 " " 7.6 5 " " 7.8 4 " " 8.	2 were pH 6. 1 was " 6.8 1 " " 7. 2 were " 7.6	1 was pH 6.6 2 were " 6.8 19 " " 7. 8 " " 7.2 1 was " 7.4	1 was pH 6.6 2 were " 6.8 1 was " 7. 5 were " 7.2 8 " " 7.4 2 " " 7.6 8 " " 7.8 1 was " 8.

The hydrogen-ion concentration of cultures explanted into media having different hydrogen-ion concentrations (pH 6.0, 7.0, 8.0, and 9.0). The cultures which failed to grow were usually tested after 48 hours, but in some instances not until after three or four days. The age at which the cultures exhibiting extensive growth were tested varied from 24 hours to 14 days.

The final hydrogen-ion concentration was obtained by testing cultures just after the cells had died or while one or two still remained alive. This occurred between four days and four weeks, usually at the end of 15 days.

1 per cent dextrose seemed to be dependent upon the rapidity with which the formation of acid took place. When death took place, the cells appeared quite different from those in 0.25 per cent to 0.5 per cent sugar, as vacuolization did not occur nor did the cells round up; instead they became coagulated, retaining their size and shape somewhat as skeleton forms. The cultures that died after a few days of growth had already become acid (pH 6.0), while those that still exhibited good growth when tested, even after a much longer period of time (10-14 days), had not yet done so.

The final hydrogen-ion concentration of the tissue cultures depended more upon the amount of dextrose added to the

TABLE II

Media	No. of cultures	Final H-ion concentration of culture
Without dextrose pH 6.8.....	1	pH 7.
" " " "	5	" 7.2
" " " "	2	" 7.4
" " " "	2	" 7.6
" " " 8.	3	" 7.2
" " " "	4	" 7.4
" " " "	3	" 7.6
Cultures in media without dextrose	20	Average final pH=7.35
With 1% dextrose pH 6.8	2	pH 6.
" " " " "	3	" 6.2
" " " " "	1	" 6.4
" " " " "	4	" 6.6
" " " " 8.	1	" 6.
" " " " "	1	" 6.2
" " " " "	4	" 6.4
" " " " "	3	" 6.6
" " " " "	1	" 6.8
Cultures in media with 1% dextrose	20	Average final pH=6.39

The final hydrogen-ion concentration of cultures explanted into media to which no dextrose was added and into media containing 1 per cent dextrose.

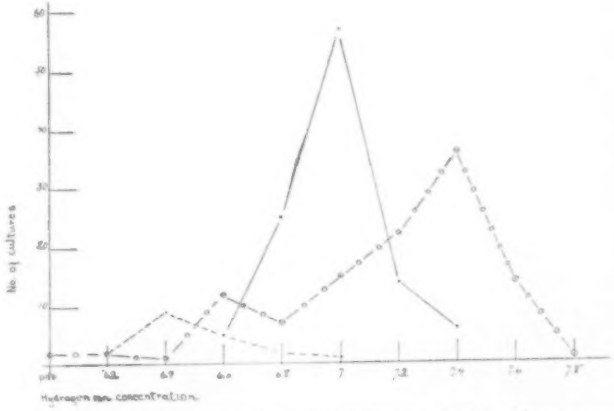

CHART I.—The hydrogen-ion concentration of 236 cultures explanted into normal Locke-Lewis solution.
- - - - - - - - - (broken line) represents the hydrogen-ion concentration of the cultures which failed to grow; ———— (smooth line) that of cultures which were tested when the growth was extensive; o—o—o—o (dotted line) that of cultures which grew well but were not tested until they had degenerated.

Locke-Lewis solution than upon the original hydrogen-ion concentration of the medium. This is shown in Table II.

DISCUSSION

From the work reported in this paper it would seem that the optimum H-ion concentration for growth *in vitro* of embryonic connective tissue cells of a 9-day chick lies between 6.8

and 7.0. The question immediately arises, Why is the optimum H-ion concentration not 7.4, as it is in the blood of an adult chicken? Although not sufficient cultures were tried at a given pH to make it possible to decide this question, the wide range in which tissue cultures grew would make it appear plausible that growth can occur as well at pH 7.4 (same as blood) as at pH 6.8 to 7.0. However, it should be borne in mind that we are dealing with embryonic tissue, more capable, perhaps, of adapting itself to the experimental environment than are the adult cells. This may account for the wide range of H-ion concentrations in which the cells grow. As stated above, the younger the embryonic tissue the higher the percentage of growth in more acid media. Aggazzotti (1913) has shown that there is a gradual neutralization of the yolk as the embryo develops, changing from a pH 4.6 to a pH 6.4 from the first to the twenty-third day of its development. Granting this to be true, a 9-day chick embryo is developing in a more acid medium than an older one and in a less acid medium than a younger one. It seems reasonable that the optimum pH for a 9-day chick might be lower than for the adult animal and that this optimum would be the same as that of the yolk-sac at each respective stage of development.

The carbohydrate (dextrose) metabolism of embryonic connective tissue is seemingly very similar to that of bacteria. In a medium without dextrose, the pH increases as it does with most bacteria grown on ordinary dextrose-free medium, while with 0.25 per cent to 0.5 per cent of dextrose the H-ion level remains the same or swings a little to the acid or basic side from the original fluid. The two factors that influence this difference are the size of the drop of medium (buffer) and the condition and size of the explant. However, in a medium of 1 per cent dextrose, the entire buffer effect is used up by the acid produced from the dextrose, and the H-ion concentration is always more acid than the original solution. These results are strikingly parallel to those found in the study of bacteria under similar conditions.

Summary

Tissue cultures of chick embryos explanted into Locke-Lewis solution of a H-ion concentration between 5.5 and 9.0 exhibited growth. The medium most favorable for growth was one having a hydrogen-ion concentration about 6.8 to 7.0. The addition of dextrose to the medium was necessary for the healthy growth of cells over a period of time longer than three days. While all cultures in solutions containing up to 5 per cent dextrose exhibited growth, those in solutions containing between 0.5 per cent and 1 per cent had the greatest proliferation of cells and remained healthy for the longest period of time. Cultures that failed to grow were usually slightly acid, while cultures exhibiting extensive growth, when tested, were as a rule nearly neutral.

The final hydrogen-ion concentrations of the cultures depended upon the amount of dextrose in the medium. Those in solutions to which no dextrose had been added were pH 7.0 to 7.6, while those to which 2 to 5 per cent dextrose had been added were often pH 5.6 to 6.4.

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THE RELATION OF H-ION CONCENTRATION TO SPECIFIC PRECIPITATION

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The purpose of this article is to present the results of a series of experiments designed to determine the relation of specific precipitation to the H-ion concentration of the solution in which the antigen-antibody reaction takes place.

The earlier experiments of Michaelis and Davidson[1] were made with combinations of sheep serum as antigen and immune rabbit serum as antibody. The H-ion concentration of the medium in which the precipitation reaction occurred was varied by the use of solutions of sodium acetate and acetic acid. Since non-specific protein precipitation occurred, their results were subject to an error dependent on the difficulty of determining the amount of such precipitation, as may be readily observed in their protocols. They found that specific precipitation occurred between [H] 3×10^{-6} and [H] 6×10^{-8} when the antigen was employed in small amounts. If the dilution of antigen was less, however, precipitation occurred in the H-ion range of primary and secondary phosphate solutions, viz., from pH 5 to pH 9. They did not attempt to define the exact range of [H] in which specific precipitation occurred.

In the series of experiments recorded below crystallized egg albumen was employed as antigen. A precipitating serum was produced in rabbits by three daily intravenous injections of 0.01 gm. of antigen in physiological salt solution. At the end of about three weeks the titer of the immune serum

[1] Michaelis and Davidsohn, Die Abhängigkeit spezifischer Fällungsreaktionen von der Wasserstoffionenkonzentration. Biochem. Ztschr., Berlin, 1912, XLVII, 59.

was usually greater than 1 : 100.000. The hydrogen-ion concentration of the mixtures of antibody and antigen was altered by the addition of various amounts of M/1 NaOH and M/1 H_3PO_4. Since neither of these is a protein precipitant, confusion due to non-specific precipitation was avoided. Furthermore, wide variations of the hydrogen-ion concentration were possible. The NaCl concentration was kept constant by the use of 0.85 per cent NaCl as diluent for antigen.

PROCEDURE

Three parallel rows of 20 small test-tubes were set up and into each tube 0.1 c. c. of immune rabbit serum was introduced. The precipitin titer of the serum was greater than 1 : 100,000 in each experiment. 0.2 c. c. of a mixture of M/1 NaOH and M/1 H_3PO_4 was added to each tube in such a fashion that tube 1 of each series contained a solution whose pH was about 4 and tube 20 of each series contained a solution of about pH 10. The pH of the solutions in the intermediate tubes of each series ascended from 4 to 10 according to the typical curve. Antigen was next added as follows: To each tube of series 1, 0.1 c. c. of a 1 : 16.500 solution of egg albumen. To each tube of series 2, 0.1 c. c. of a 1 : 8250 solution. To each tube of series, 3, 0.1 c. c. of a 1 : 1650 solution. The tubes were shaken and placed in a water-bath at 37° for 30 minutes. Certain controls were prepared as follows:

1. pH solutions plus solutions of egg albumen in the same amounts as used in the experiment.

2. pH solutions plus normal rabbit serum in the same amounts as used in the experiment.

3. pH solutions plus normal rabbit serum plus antigen in the same amounts as used in the experiment.

At the end of 30 minutes the results were read and the relative amount of precipitation noted. The pH of the tubes to right and left of the tube in which precipitation was just visible was determined by colorimetric methods, the dyes recommended by Clark and Lubs being employed.

RESULTS

A series of experiments similar to those outlined above were performed and the results were fairly constant. Although there was occasionally difficulty in detecting minimum amounts of precipitation, the end-point was sharp unless the pH of the solution in adjoining tubes differed by less than 0.5. In general, precipitation was marked in the tubes which contained solutions whose pH ranged from 9.5 to 4.5 inclusive. The degree of dilution of the antigen was without appreciable effect unless this was greater than the precipitin-titer of the serum or low enough to be affected by the phenomenon of inhibition. Furthermore, although accurate methods for measuring the amounts of precipitation were not employed, there was apparently no more precipitate present in the tubes whose pH was near the isoelectric point of serum globulin (5.4) or of crystalline egg albumen (4.8).

In a further series of experiments similar to those outlined above, antigen and antibody were allowed to come in contact, with consequent precipitation, before the introduction of acid-alkali mixtures. The precipitate dissolved rapidly in the tubes which contained a mixture more alkaline than pH 9.5 or more acid than pH 4.5. In the tubes in which the H-ion concentration was between $10^{-4.5}$ and $10^{-9.5}$ inclusive the precipitate persisted, apparently unaltered.

CONCLUSIONS

Specific precipitation with the solutions employed above occurred between pH 4.5 and pH 9.5 inclusive. Moreover, specific precipitates permitted to form in a neutral medium were dissolved if the pH was reduced to less than 4.5 or increased to greater than 9.5.

NOTES ON NEW BOOKS

Ephraim McDowell (1771-1830), "Father of Ovariotomy" and Founder of Abdominal Surgery, with an appendix on Jane Todd Crawford. By AUGUST SCHACHNER, M. D., F. A. C. S., Louisville, Kentucky. (*J. B. Lippincott, 1921.*)

The discovery of vaccination against smallpox, the discovery of anesthesia, and the Listerian doctrine of antisepsis, were perhaps more dramatic in their presentation and reception by the world, but they were surely not more than coordinates in importance with McDowell's heroic effort in opening up the whole realm of abdominal surgery, which is the theme of an admirable life of Ephraim McDowell by August Schachner, of Louisville, Kentucky.

In this delightfully written work we have all the data for a complete history of one of our great medical pioneers, if not, indeed, the greatest. It has taken years of patient research to collect all the facts of the life of this great doctor frontiersman, and of his heroic patient, Jane Crawford, so that Schachner's work is conspicuous for its untiring industry, and stands out as a model for future historians.

Our author is quite clear and is fully justified in pointing out that McDowell was not merely the first ovariotomist of the world, who thus not only inaugurated a wholly new procedure, in which for a couple of generations he easily outstripped all competitors in his low death rate, but that he by this act of opening the peritoneum revealed the whole nascent realm of abdominal surgery.

Just one hundred and twelve years have passed since in December, 1809, Jane Crawford laid herself, a willing sacrifice, upon the table in McDowell's house, and endured the operation of cutting out a large ovarian tumor, confessedly an "experiment," repeating the Psalms as the doctor proceeded with his bold work. All precedents and the advice of all the eminent teachers of the time were against the innovation and, had it failed, what opprobrium would have fallen upon our progenitor's head; but since this rivulet started in the mountains of Kentucky, all the world has added its tributaries until it has become a mighty stream, destined still to enlarge and to flow on as long as man lives on earth and is subject to disease.

Europe at first disbelieved, then opposed, and then adopted the innovation, and last of all tried to rob the backwoodsman of his credit by faking an earlier operator. But to-day, McDowell's reputation is unassailable, and all rejoice to join with Schachner in placing laurels upon his worthy brow.

A further dramatic offset to the *mis en scène* is found in the objection to the operation raised by McDowell's nephew associate who lent only grudging aid in the rash procedure.

Alas, that we have so few such classics in our American medical literature as this excellent book. May it reach many of our doctors.

H. A. K.

The Oxford Medicine. By Various Authors. Edited by Henry A. Christian and Sir James Mackenzie. (*Oxford University Press, London and New York, 1921.*)

An inherently unfortunate feature of a system of medicine is this that for better or for worse it seems necessary to include all the diseases in the domain of the internist. The treatment of certain of the subjects, therefore, which are already covered by classical and altogether satisfactory monographs is foredoomed to inferiority. In the fourth volume of the Oxford Medicine one finds several sections which are excellent in themselves, but still suffer in comparison with previous well-known and readily accessible treatises. One may mention especially the chapters on the spleen, on the muscles, on the bones, and on sepsis. On the other hand, many of the articles are well worth while. Allbutt writes on gout in the older clinical style, leaving the chemical side to his associates; Longcope gives a brief but thorough summary of Hodgkin's Disease; Joslin on diabetes is always interesting, and Rountree summarizes the newer points of view in diabetes insipidus. The infectious diseases are well handled, but in a conventional way; the article on pneumonia by Irons is particularly valuable as a summary of the bacteriological side of this malady. The sections on industrial medicine are of interest, especially the introductory article on the physiology and pathology of work by Cecil and Katherine Drinker. On the whole the volume seems a useful one.

A. L. B.

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